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CARCINOMA OF THE PROSTATE

CORRELATION BETWEEN THE HISTOLOGIC OBSERVATIONS AND THE CLINICAL COURSE

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LOS ANGELES

Attempts by the pathologist to determine the degree of malignancy of cancer by microscopic appearances are routine in some pathologic services. The frequency of such attempts and of requests by clinicians for such reports varies with the organ involved. In our experience such requests have not been frequent with prostatic cancers, and rarely if ever have we attempted to assign a numerical grading to one of these.

The reasons for routine reporting of the histologic grades of such cancers as carcinoma of the skin, the lip and the rectum and for the much less frequent attempts at grading carcinoma in some other anatomic areas are not entirely clear. Conceivably the more complex character of the changes in carcinoma of the prostate, for instance, may have deterred pathologists from assuming such responsibility. Possibly the hopelessness of cure of carcinoma of the prostate in contrast to certain more accessible tumors may be a factor.

It is of interest that Virchow,[1] the father of "cellular pathology," from the first had a rather clear conception of the fact that certain groups of cancers varied in degree of malignancy. In his well known lectures in the 1850's he made unmistakable statements of this point of view. For illustration, "*Cancer* is not malignant because it contains heterologous cells, nor *cancroid* benignant because its cells are homologous—they are both malignant and their malignity *only differs in degree.*" (The italics are ours.)

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1. Virchow, R.: Cellular Pathology, translated by F. Chance, New York, Robert M. DeWitt, 1860, p. 530.

Hansemann,[2] in 1893, was the first to suggest the practicability of recognizing grades of clinical malignancy based on histologic degrees of abnormality. He used the term "anaplasia," now used as practically synonymous with "undifferentiation," as descriptive of the essential quality of cancers. Later, in 1902, he again published a report of actual attempts at grading cancer, showing statistically that it is practically possible. He pointed out that highly anaplastic cancers almost always recur and metastasize and that those showing a lesser grade of anaplasia sometimes are cured. His work attracted little attention, and it was not until 1920 (eighteen years later) that Broders [3] published his first paper on the grading of carcinoma of the lip.

Broders has applied the method to other forms of cancer, including carcinoma of the skin, the rectum and the esophagus. Greenough [4] and Haagensen [5] have published notable work on grading carcinoma of the breast. Mahle applied the method to carcinoma of the endometrium, and Martzloff made widely recognized contributions to the grading of carcinoma of the cervix.

Broders has held consistently to the idea of four divisions in his grading, while in several of the original studies a classification into three grades had been adopted as more practical. Examples of this may be found in the reports of Greenough and Haagensen on carcinoma of the breast and in Martzloff's work on the cervix uteri.

Carcinoma of the prostate, despite its importance and appallingly high incidence in men past 50, has apparently not been adequately studied from this particular point of view.

Kahler [6] in his important study of carcinoma of the prostate divided adenocarcinoma of the prostate as studied microscopically in 124 cases into four grades, according to Broders' classification, but did not describe in detail the criteria or the method as applied to the prostate.

Judd, Bumpus and Scholl,[7] in 1921, divided carcinoma of the prostate as observed in a series of 100 cases into two grades or types.

Ferguson [8] in a study of 501 cases collected from various sources divided carcinoma of the prostate into three distinct types as distinguished by the use of an arbitrary clinical index of malignancy. The factors constituting this clinical index are: age, duration of symptoms, amount of residual urine and extent of the disease. The statement is

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2. von Hansemann, D. P., cited by Haagensen, C. D.: Am. J. Cancer **19**:285, 1933.

3. Broders, A. C.: J. A. M. A. **74**:656, 1920.

4. Greenough, R. B.: J. Cancer Research **9**:453, 1925.

5. Haagensen, C. D.: Am. J. Cancer **19**:285, 1933.

6. Kahler, J. E.: J. Urol. **41**:557, 1939.

7. Judd, E. S.; Bumpus, H. C., Jr., and Scholl, A. J., Jr.: S. Clin. North America **1**:1279, 1921.

8. Ferguson, R. S.: Am. J. Cancer **16**:782, 1932.

made that "microscopic grading closely parallels the clinical classification" and that the basis of the microscopic classification is the presence or the absence of alveolar arrangement and of anaplasia. No indication of a statistical study of the individual microscopic features and their relation to the four clinical groups described is apparent in the report.

In the present study we used 100 consecutive cases of carcinoma of the prostate which were studied between 1925 and 1936 and which conformed to the following requirements: 1. Satisfactory microscopic sections were available for a detailed histologic study. 2. There was a record of a definite time of onset of symptoms produced by the carcinoma of the prostate. 3. If the patient died, death occurred more than one month after surgical treatment. This requirement eliminated operative deaths. 4. There was a follow-up record until death or for a survival period of five years or more after the onset of symptoms. The patients were both private and charity patients, and the latter were seen by different urologists. Autopsy was done in 25 of the 100 cases. Nine of the patients are still living.

HISTOLOGIC CRITERIA

Eight chief aspects of the tumor's structure and its cells were selected as presenting possible valid criteria for grading: (1) acinous structure, (2) cell structure, (3) density of cytoplasm, (4) nuclear characteristics, (5) presence of nucleoli, (6) mitotic figures, (7) fibrosis and (8) inflammation.

The structure of the tumor and its cells were described in each case. The method of recording the description, as shown in the following tabulations with respect to each of these criteria, consisted in grading each histologic feature on a scale of four divisions. In general, grade 1 represented the closest approach to normal, while grade 4 represented the extreme degree of abnormality and undifferentiation.

An additional procedure in this analysis was made necessary by the well known tendency of prostatic carcinoma to vary in appearance in different parts of the same tumor. Three of the structural features, i. e., acinous formation, cell shape and nuclear size, were recorded not only by grade of abnormality but also by the proportion of each grade present in a given cancer.

The eight histologic features examined, and the rules for grading each, are as follows:

Acinous Structure.—If one assumes that the primary feature of carcinoma in glandular tissue is loss of differentiation, it is obvious that the highest grade of malignancy is indicated by complete loss of acinous structure and the lowest by the nearest approach to normal acinous configuration.

Grade I. Large folded acini or acini with papillary intra-acinous growth (fig. 1 *A*). Variations of this type toward two extremes were

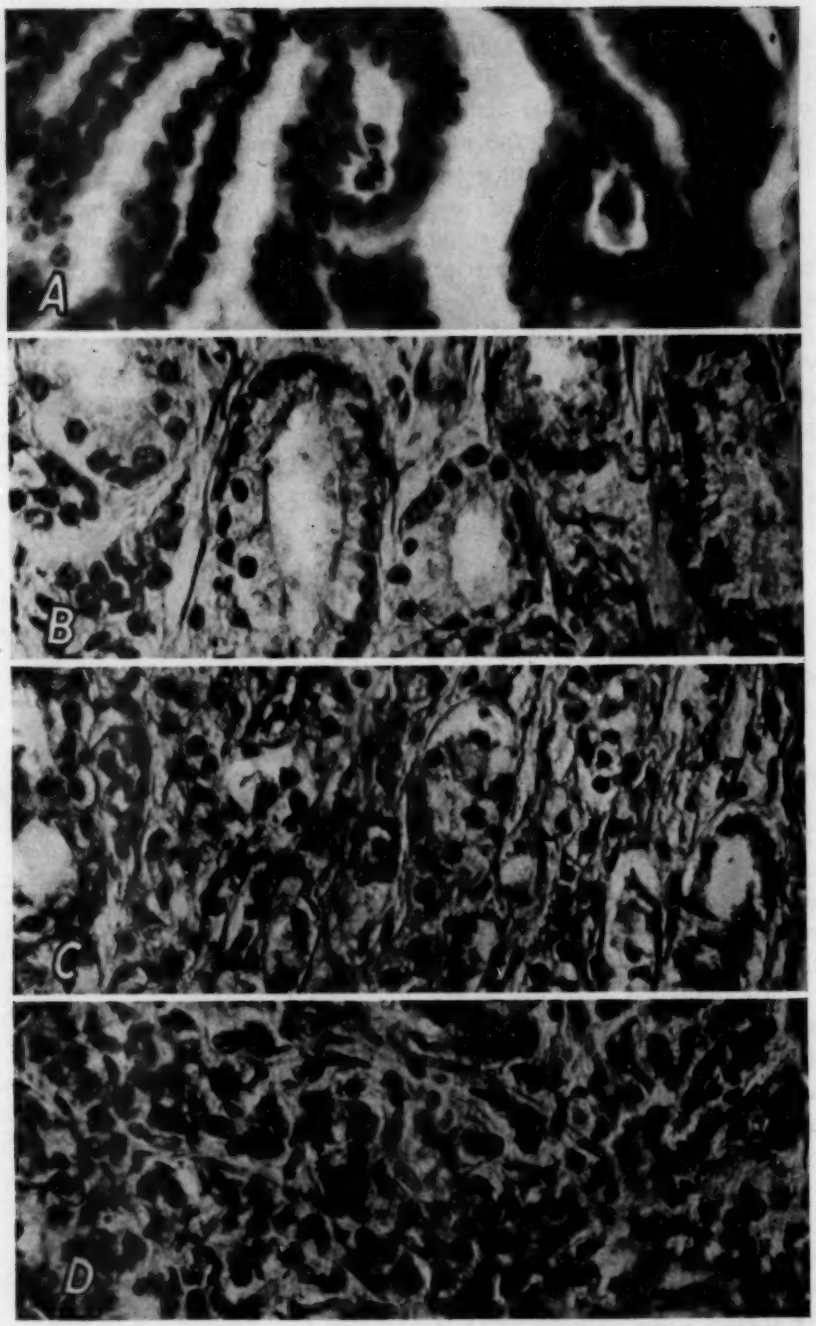

Fig. 1.—Adenocarcinoma of the prostate; × 400. *A, B, C* and *D* show grades I to IV, respectively, of malignancy as estimated on the basis of abnormality of acinous structure. With increase in malignancy the acini are seen to become simplified (*B*), then to become indistinct (*C*) and finally to disappear (*D*).

encountered. Some of the less plainly carcinomatous structures approached the appearance of noncancerous hyperplasia. In such an instance the diagnosis of carcinoma was made on the basis of cellular and nuclear anaplasia if possible; otherwise the classification depended on the association with nearby structures that were more obviously carcinomatous. On the other hand, the papillary intra-acinous growth sometimes became complex, producing broad lacework patterns, in which the anastomosing papillary projections formed a filigree of large or small secondary acini. This type was graded on the basis of the structure of the secondary acini. If these were large, folded and well formed the classification was in grade I. Smaller and less well formed secondary acini were graded II or III.

Grade II. Smaller, simple acini with definite lumens (fig. 1 *B*).

Grade III. Very small or incomplete acini, having usually no more than a suggestion of lumens (fig. 1 *C*).

Grade IV. Absence of acinous structure (fig. 1 *D*).

Cell Structure.—This characteristic was graded according to the degree of departure from the usual typical columnar shape of the prostatic gland cell.

Grade I. Definitely columnar cells.

Grade II. Shorter, broader cells—cuboidal cells.

Grade III. Rounded or polygonal cells.

Grade IV. Cells without regular shape and with a small or negligible proportion of cytoplasm as compared with the nuclear size.

Cytoplasm.—An attempt was made to classify the cells according to the density of their cytoplasm. The normal prostatic cell usually has relatively clear cytoplasm; therefore, the grades were arranged in increasing order of density.

Grade I. Clear cytoplasm.

Grade II. Slight staining of cytoplasm.

Grade III. Moderate staining of cytoplasm.

Grade IV. Deep staining of cytoplasm.

Nuclei.—These were classified principally on the basis of size, with secondary consideration of shape, texture and variation of appearance.

Grade I. Small nuclei, 5 microns or less in greatest diameter. These were usually dense and smooth textured (fig. 2 *A*).

Grade II. Moderately large nuclei, 5 to 7.5 microns in greatest diameter. These were usually moderately granular with some variation in size, shape and staining affinity.

Grade III. Larger nuclei, 7.5 to 10 microns in greatest diameter.

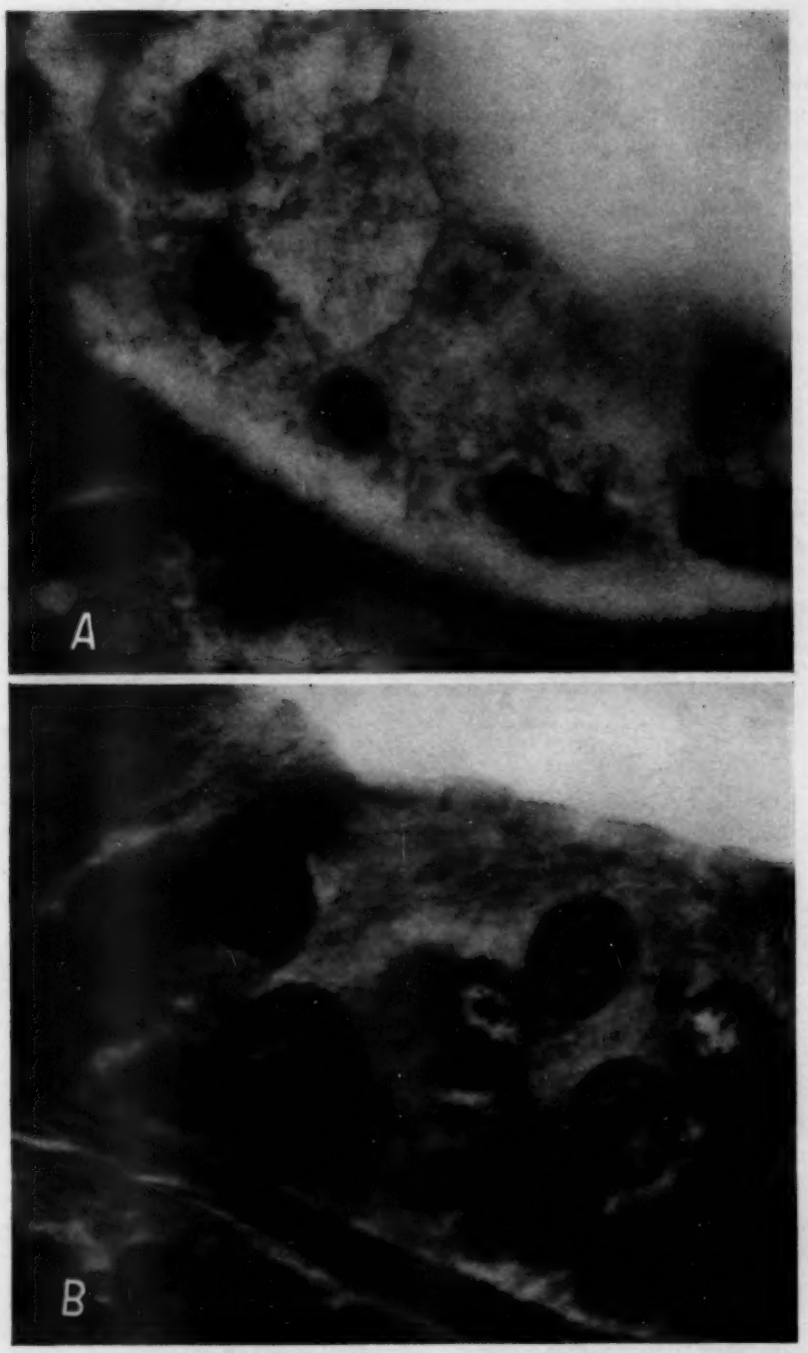

Fig. 2.—Adenocarcinoma of the prostate. *A* and *B* (each × 1,800) show nuclei of grades I and IV, respectively. A mitotic figure is included in *B*. The two extremes of density of cytoplasm are also shown.

Grade IV. Very large nuclei, 10 microns and over in greatest diameter (fig. 2*B*).

Nucleoli and Mitotic Figures.—These were each graded according to frequency of occurrence as follows:

Grade I. None seen.

Grade II. Present in less than one tenth of the fields examined.

Grade III. Present in one tenth to one half of the fields examined.

Grade IV. Present in more than one half of the fields examined.

Fibrosis and Inflammation.—These were each classified in four grades as follows: absent, mild, moderate and severe.

DISTRIBUTION OF CANCERS IN HISTOLOGIC GRADING

The number of cancers falling into each of the four grades varied according to the criterion used. In the groups graded by acinous structure, cell structure and nuclei, respectively, the distribution was quite similar. Half or more of the specimens were found in grade III, with approximately equal division of the others between grades II and IV. The numbers classified in grade I according to these three criteria were so small, ranging from 2 to 7, that these specimens were not considered separately but were combined with those in grade II.

Distribution of cancers according to density of cytoplasm found nearly all the specimens approximately equally divided between grades II and III, i. e., showing slight or moderate density.

In the examination of the nucleoli, nearly one fourth of the specimens failed to show these structures. It is possible that in some of these fixation was not sufficiently prompt to preserve the nucleoli. Nearly half the cancers showed the presence of a few nucleoli, another one fourth showed moderate numbers of nucleoli, while only 8 had nucleoli in more than half the fields.

Mitotic figures were not numerous. In about one half of the cancers no mitotic figures were recognized. The remainder showed only occasional mitotic figures. Only 5 cancers showed mitotic figures in more than one tenth of the fields. No specimens were found in grade IV in this criterion.

Fibrosis was found to be present in mild degree in nearly half the specimens. Moderate fibrosis was observed somewhat less frequently, while severe fibrosis was present in only 6. Thirteen specimens showed no fibrosis.

Inflammation was also present in mild degree in about half the specimens, but was absent in one third of them. A few examples of moderate inflammation and one of severe inflammation were found.

Composite Grade.—The distribution of the 100 specimens according to a composite grade (obtained by combining criterion grades as described in the following section) showed 2, 18, 62 and 18 of the cancers in grades I, II, III and IV, respectively. In the following comparisons with clinical data, the 2 cases in grade I are combined with those in grade II.

CLINICAL EVALUATION OF CRITERIA

After the 100 cancer specimens had been graded according to the plan just described, the histologic and the clinical data were compared for the first time. The apparent significance of each of the eight criteria was judged by the degree of correspondence between the histologic grade of carcinoma and the clinical grade as indicated by survival time and incidence of recognized metastasis.

The correlation was made not only with each of the eight criteria but also with a composite or average grade obtained by combining the histologic grades for acinous structure, cell structure and nuclei. These three criteria were chosen as the basis of the final composite grade for each case because their correspondence with the clinical course, as will be noted in the following analysis, appears to be satisfactory and definitely superior to that of the other criteria. The clinical data and their relation to the histologic grade may be summarized as follows:

Survival Time.—Average survival time shows a marked decrease as histologic malignancy increases when grading is based on each of the three criteria, acinous structure, cell structure and nuclei. The same relationship is noted with the composite grade, so that a survival time of five and four-tenths years in grades I and II (combined) decreases to two and two-tenths years in grade IV.

No definite relation to length of survival was found with the other criteria.

The longest and the shortest survival time in each grade were also recorded. The longest survivals were eighteen and a half, thirteen and nine years in composite grades I-II, III and IV, respectively.

Incidence of Metastasis.—The cases in which information concerning the occurrence of metastasis was obtainable were found to be distributed in a consistent way when classified according to the composite histologic grade and each of its three component criteria. The distributions according to other criteria showed no consistent arrangement.[9] The percental

9. The distribution according to fibrosis showed an incidence of metastasis of 23, 25, 35 and 50 per cent in grades I to IV, respectively. The apparent 50 per cent occurrence in the group with severe fibrosis may not be completely significant, since there were only 6 cases so classified. However, there seems to be a trend toward increase of metastatic spread from the more fibrous tumors.

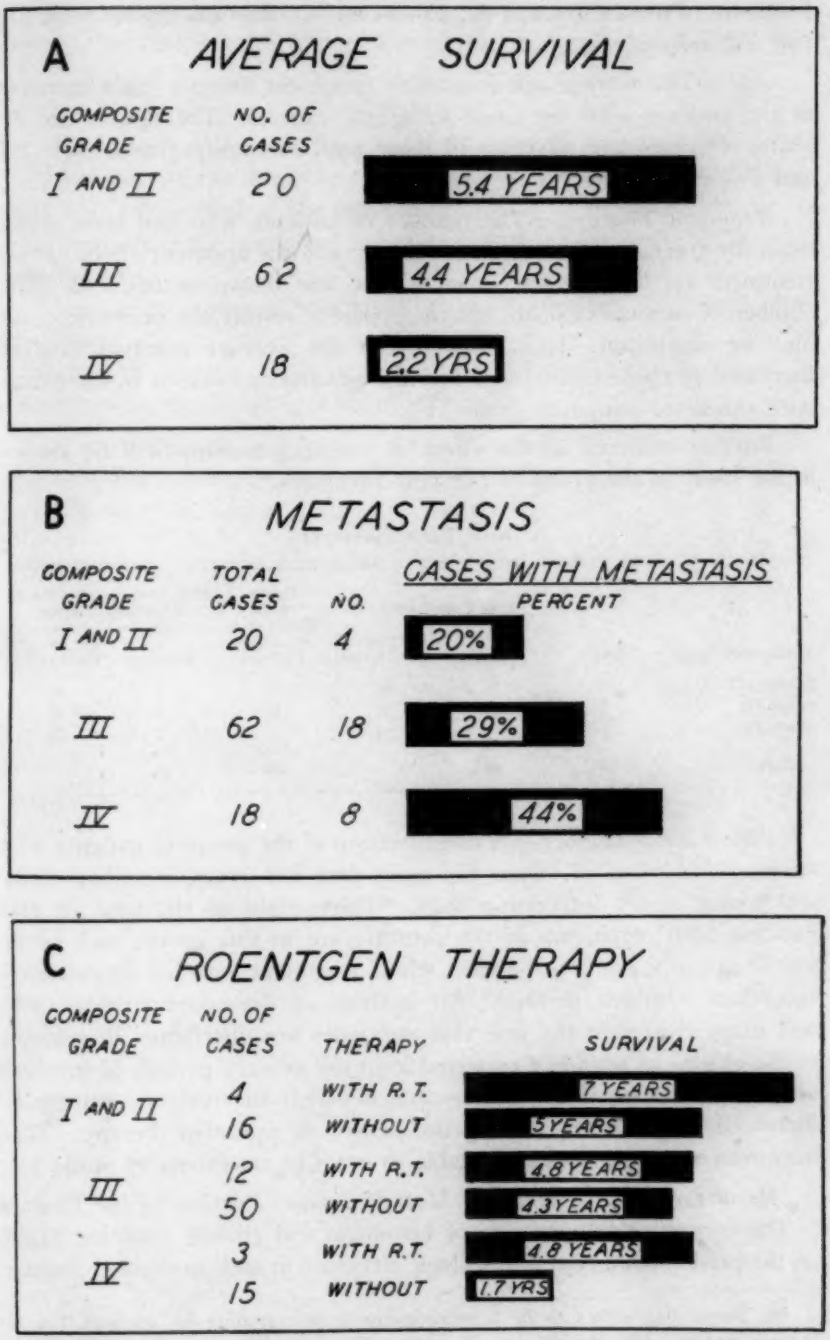

Fig. 3.—Three graphic charts to show the relation of the histologic grade of malignancy to the survival time (*A*), the incidence of metastasis (*B*) and the effect of roentgen therapy (*C*).

incidence of metastasis was 20, 29 and 44 in composite grades I-II, III and IV, respectively.

Age.—The average age at onset of symptoms shows a slight decrease in the patients with the more malignant cancers. The figures are 70 years, 69 years and 67 years in those with composite grades I-II, III and IV, respectively.[10]

Roentgen Therapy.—The number of patients who had been systematically treated with roentgen radiation and the apparent effect of this treatment on the average survival time are shown in figure 3. The number of patients is small, but the apparent results are interesting and may be significant. It is noticed that the average survival time is increased in those treated and that the greatest increase is in the group with cancer of composite grade IV.

Further evidence of the effect of roentgen therapy will be shown in the study of the group of five year survivors.

Five Year Survivors

		Five Year Survivals		Cases with Systematic	Five Year Survivals with Roentgen Therapy	
Composite Grade	Cases	Number	Per Cent in Each Grade	Roentgen Therapy	Number	Per Cent in Each Grade
Grades I-II.....	20	11	55	5	4	80
Grade III.....	62	26	42	12	8	67
Grade IV.....	18	1	5.6	3	1	33
Total.....	100	38		20	13	

Five Year Survivors.—A consideration of the group of patients who survived the onset of cancer for more than five years, including those still living, yields interesting facts. Thirty-eight of the total of 100 patients with carcinoma of the prostate are in this group, and 13 of the 38 are in a group of patients whose treatment included an extended course of roentgen therapy. An analysis of the accompanying table will make clear that the five year survivors are distributed in relation to the grades as would be expected from the average periods of survival already noted. It also is obvious that five year survivals are materially increased in the group having the benefit of radiation therapy. This improvement is particularly notable in cases of carcinoma of grade IV.

Results of Grading Only the Most Malignant Portions of the Tumor.—The foregoing comparisons of histologic and clinical data are based on the predominant type of histologic structure in each specimen. Similar

10. There also seems to be a relationship to the grading by nucleoli, but in reverse order. The figures are 69 years, 68 years, 70 years and 72 years in composite grades I, II, III and IV, respectively.

comparisons made with grades based only on the most malignant elements present in each tumor showed no significant correlations.

SUMMARY

A histologic grade of carcinoma of the prostate based on the degree of abnormality of the acini, the cells and the nuclei is of use in predicting the length of survival of the patient.

The grade of the carcinoma indicates the probability of the occurrence of metastasis.

The higher grades of carcinoma occur at slightly earlier ages than the lower.

Roentgen therapy appears to lengthen survival time, more so in patients with the higher grades of carcinoma.

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COCCIDIOIDOMYCOSIS IN STATES OTHER THAN CALIFORNIA, WITH REPORT OF A CASE IN LOUISIANA

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The observation of a fatal case of coccidioidomycosis of the granulomatous type in Louisiana prompted us to make a survey of the literature with particular reference to collecting the recorded cases which had been observed in the United States exclusive of California. Our chief interest was to determine, if possible, whether there was any evidence for the view that the disease is spread by migratory patients or the view that new endemic foci have developed. Both views have been expressed by authors who reported cases observed outside of California. The discovery of misquotations and of duplicate reports of the same cases recorded as reports of different cases by some reviewers also made it imperative to collect the cases from the original sources.

SURVEY OF THE LITERATURE

Most authors who have commented on the subject have stated that about 80 per cent of the cases recorded in the world's literature have been observed in California. Reisman and Ahlfeldt [1] in 1927 collected 87 cases from the literature; the majority of the patients had been residents of California and had been observed in California; 5 had been observed in the United States outside of California. Tomlinson and Bancroft [2] in 1928 collected 88 cases in the United States; 75 of the patients had been observed in California and 13 in other states. No references to the literature pertaining to this review were given; hence we were unable to check these cases by the original reports. Since 1928 the disease has been reportable in California, and hence much better data concerning the cases in California are now available. Beck,[3] who with few exceptions has been consistently misquoted, stated that of the 286

From the departments of pathology and bacteriology of the Louisiana State University School of Medicine and the Charity Hospital of Louisiana.

1. Reisman, D., and Ahlfeldt, F. E.: Am. J. M. Sc. **174**:151, 1927.

2. Tomlinson, C. C., and Bancroft, P.: J. A. M. A. **91**:947, 1928.

3. Beck, D.: Special Bulletin 57, California State Department of Public Health, 1931.

recorded cases 254 (89.5 per cent) had been observed in California and 16 in other states of the Union. Of these 254 cases, 128 were recorded in the literature. Duckett and Fredeen [4] referred to Beck's [3] report and stated: "Since this time at least 26 sporadic cases have been reported." We were unable to determine from the article where these cases had been observed. Dickson,[5] quoting a California public health report bulletin,[6] stated that 450 cases of coccidioidal granuloma had been observed in California to July 1, 1936.

In our review, we accepted as proved cases (1) those in which typical spherules showing endosporulation without budding or without formation of mycelia had been demonstrated in human tissue and exudate, (2) those in which a pure culture of the organism had been obtained the identity of which was substantiated by its typical appearance in human tissue or exudate or by animal experiments.

We were able to collect 26 cases which had been observed outside of California (table).

The onset of illness in 6 of these patients occurred while they were in California or shortly after they had been there; 20 of the patients never had been in California. Because of the peculiar nature of the organism, which showed both endosporulation and budding in tissue, we excluded Beaver and Furrer's [7] excellent report of an infection simulating coccidioidal granuloma, which they observed in Minnesota. Reference has also been made by Carter [8] to a case in Virginia, by Smith and Waite [9] to several cases in Texas, by Brown [10] to 2 cases in Arizona, by Phillips [11] to 8 cases in Arizona and by Caldwell [12] to 2 cases in Texas in addition to the 3 which he reported. All of these are excluded from this review because the evidence of infection is not conclusive. It is admitted that some of these cases with the diagnosis based on a positive cutaneous reaction to coccidioidin [13] probably are instances of coccidioidomycosis without granulomatous manifestations. Smith's [14] estimate, based on his excellent survey, that between 8,000 and 10,000 persons have suffered from coccidioidomycosis in Kern and Tulare counties of California makes it appear quite probable that these cases are authentic and should be seriously considered.

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4. Duckett, T. G., and Fredeen, R. C.: J. Kansas M. Soc. **37**:111, 1936.
5. Dickson, E. C.: Am. Rev. Tuberc. **38**:722, 1938.
6. Weekly Bull. California Dept. Pub. Health **16**:2, 1937.
7. Beaver, D. C., and Furrer, E. D.: J. Lab. & Clin. Med. **18**:329, 1933.
8. Carter, R. A.: Am. J. Roentgenol. **25**:715, 1931.
9. Smith, L. M., and Waite, W. W.: Southwestern Med. **18**:305, 1934.
10. Brown, O. H.: Southwestern Med. **23**:131, 1939.
11. Phillips, E. W.: Southwestern Med. **23**:48, 1939.
12. Caldwell, G. T.: Texas State J. Med. **28**:327, 1932.
13. Brown.[10] Phillips.[11]
14. Smith, C. E.: Am. J. Pub. Health **30**:600, 1940.

Cases of Coccidioidomycosis in United States Outside of California

Case	Author	Year	Race	Sex	Age	Occupation	Source	Where Observed	Tissue	Culture	Animal	Patient Died	Lesions	
													Primary	Secondary
1	MacNeal and Hjelm [15a], Morris [15b]	1913	W	M	37	Physician	Texas–Ill.	N. Y.	0	+	+	+	Cutaneous ? Pulmonary ?	Systemic
2	Lipsitz, S. H.; Lawson, G. W., and Fessenden, E. M.: J. A. M. A. **66**: 1365, 1916. Lipsitz, S. T.: J. Missouri M. A. **13**: 534, 1916	1916	N	M	28	Pullman porter	Denver–St. Louis	Mo.	+	+	+	+	Pulmonary	Subcutaneous abscess
3	Lynch, K. M.: South. M. J. **13**: 246, 1920	1920	N	F	45	Housewife	S. C.	S. C.	+	0	0	+	Pulmonary	None
4	Burkhead, C. R.: J. Kansas M. Soc. **22**: 101, 1922	1922	Not stated			Not stated	Probably Kan.—not stated	Kan.	+	0	0	+	Cutaneous	Involving lungs, lymph nodes, joints
5	Hirsch, E. F.: J. A. M. A. **81**: 375, 1923	1923	N	M	27	Pullman porter	Calif.	Ill.	+	+	0	+	Pulmonary	Vertebrae; psoas abscess; empyema
6	Guy, W. H., and Jacob, F. M.: Arch. Dermat. & Syph. **14**: 396, 1926; **16**: 308, 1927	1926	W	M	36	Laborer	Calif.	Pa.	0	+	+	0	Cutaneous	Subcutaneous abscess
7	Kelton, W.: Northwest Med. **26**: 92, 1927	1927	Filipino	M	23	Seaman	Wash.? Alaska ?	Wash.	+	0	0	0	Cutaneous	Osteomyelitis
8	Reisman and Ahlfeldt [1].....	1927	W	M	5	Child	N. Mex.	Pa.	+	+	+	+	Pulmonary ? (preceding diarrhea)	Involving lungs, lymph nodes, pleura; subcutaneous abscess
9	Tomlinson and Bancroft [2].....	1928	W	M	26	Medical student	Lab. infection Neb.	Neb.	0	+	+	0	Pulmonary	Subcutaneous abscesses
10	Jaffé, R. H.: Virchows Arch. f. path. Anat. **278**: 42, 1930. Tomlinson, C. C., and Bancroft, P.: J. A.M. A. **102**: 36, 1934. Zeisler, E. P.: Arch Dermat. & Syph. **25**: 52, 1932	1930	W	M	36	Aviator	Calif.	Ill.	+	+	+	+ (suicide)	Cutaneous	None
11	Jaffé, R. H.: Virchows Arch. f. path. Anat. **278**: 42, 1930	1930	Mexican	M	24	Farmer	Mexico, Colo.–Kan.; Ill.	Ill.	+	0	0	0	Bone and joint	None

12	Williams, H. B.: M. Bull. Vet. Admin. **8**: 435, 1932	1932	W	M	38	Marine	Nicaragua ? Santo Domingo ?	N. Y.	+	+	+	+	Pulmonary	None
13	Caldwell [12]	1932	W	M	33	Cafe manager	Texas	Texas	+	0	0	0	Bone and joint	None
14	Caldwell [12]	1932	N	F	19	?	Texas	Texas	+	0	0	+	Pulmonary	Pulmonary, splenic, renal
15	Caldwell [12]	1932	?	?	7 mos.	Infant	Texas	Texas	+	0	0	0	Cutaneous	None
16	Smith, L. M.: Arch Dermat. & Syph. **28**: 175, 1933	1933	?	M	63	Bricklayer	Texas	Texas	+	+	0	0	Cutaneous	Subcutaneous abscesses
17	Tomlinson, C. C., and Bancroft, P.: J. A. M. A. **102**: 30, 1934	1934	W	M	7	Child	Neb.–Texas–La.	Neb.	0	+	+	0	Cutaneous	None
18	Smith and Waite [9]	1934	Mexican	F	28	?	Texas	Texas	+	+	0	+	Pulmonary ?	Suppurative arthritis; subcutaneous abscess
19	McDonald, C.: J. Lab. & Clin. Med. **20**: 47, 1934	1934	?	M	?	War veteran	World War I (overseas)	Ala.	0	+	+	+	Pulmonary ?	Not known
20	Duckett and Predeen [4]	1936	W	M	5	Child	N. Mex.–Texas–Kan.	Kan.	+	0	0	+	Cutaneous (ulcer of finger)	Cerebral, meningeal, pulmonary, adrenal
21	Farness, O. J., and Mills, C. W.: Am. Rev. Tuberc. **39**: 206, 1939	1939	W	M	15	School	Ariz.	Ariz.	0	+	+	0	Pulmonary	None
22	Farness and Mills: ibid.	1939	W	M	67	?	Ariz.?	Ariz.	+	+	0	+	Pulmonary	None
23	Storts, B. P.: J. A. M. A. **112**: 1334, 1939	1939	?	?	4	Rode in laundry truck	Ariz.	Ariz.	+	0	0	+	Meningitic	None
24	Hynes, K. E.: Northwest Med. **38**: 19, 1939	1939	Filipino	M	31	Sheepherder	Calif.	Wash.	0	+	+	0	Pulmonary	Subcutaneous abscess; lymph adenitis
25	Hynes, ibid.	1939	Filipino	M	30	?	Calif.	Wash.	0	+	+	0	Pulmonary	Abscess of neck
26	Yegian, D., and Kegel, R.: Am. Rev. Tuberc. **41**: 393, 1940	1940	W	F	25	Housewife	Calif.	N. J.	0	+	+	0	Pulmonary	None
27	Schenken and Palik (this report)	1942	N	M	33	Fruit handler	Calif.	La.	+	+	+	+	Pulmonary	Systemic

REPORT OF CASE

A Negro man, 33 years of age, was admitted to the Charity Hospital of Louisiana on March 3, 1938, complaining of "swellings" over the body, cough, fever and night sweats. About six months previously he went to California, where he was employed as a fruit handler in a Los Angeles hotel. During the first week in February 1938, while still employed as a fruit handler, he noticed a painless swelling over the back, soon followed by similar lesions over the right anterior and left posterior surface of the chest, over the sacrum and on the left forearm. Night sweats, fever and loss of weight and strength occurred concurrently. A persistent nonproductive cough developed about ten days prior to admission. He was discharged from his position because, he was told, he had tuberculosis. He returned to Louisiana.

On admission the oral temperature was 101 F., the pulse rate 90 per minute and the respiratory rate 20 per minute. The patient was emaciated, had pale conjunctivas and showed the results of poor oral hygiene. Large fluctuant subcutaneous masses, without apparent increase in the temperature of the skin, were noted in the regions mentioned in the history. They varied in diameter from 2.0 to 12.0 cm. The heart, lungs, abdomen and nervous system revealed no abnormalities.

A roentgenogram of the thorax on March 3 showed increased hilar shadows, suggestive of enlarged lymph nodes, and fine mottled shadows of increased density throughout both lung fields. The dorsal vertebrae appeared normal.

The blood showed a hemoglobin content of 70 per cent (Sahli) and 3,500,000 red blood cells and 4,900 white blood cells per cubic millimeter; a differential count revealed 76 per cent polymorphonuclear leukocytes, 20 per cent lymphocytes and 4 per cent eosinophils. The urine was negative for sugar, albumin and abnormal sediment. The Wassermann test of the blood was negative.

March 12, rounded spherules, measuring 12 to 75 microns, with a double-contoured refractile capsule and endosporulation without budding were observed in the pale yellowish gray thick purulent material aspirated from the subcutaneous abscess on the left anterior wall of the chest. A pure culture of Coccidioides immitis was obtained. Biopsy of the wall of this abscess revealed organisms in the tissues similar to those in the smear of the pus.

March 18 a roentgenogram showed an area of erosion of the border of the left scapula and a periosteal proliferation of the distal end of the shaft of the left radius.

The abscesses were emptied repeatedly and the cavities irrigated with physiologic solution of sodium chloride, followed by instillation of thymol in olive oil. Five cubic centimeters of a colloidal copper solution were injected intramuscularly every four days for one month, without improvement. He had a picket fence type of fever during his entire stay in the hospital, the temperature ranging from 99 to 104 F., with the rise usually occurring in the afternoon and evening. Death occurred April 26, 1938.

Postmortem Examination (eight hours after death).—The body was that of a well developed, markedly emaciated Negro man measuring 171 cm. in length and weighing 50 Kg. Draining sinus tracts led into subcutaneous abscesses, each of which had an edematous wall 1 to 3 cm. thick, lined by a shaggy yellowish gray necrotic membrane, and was associated with a destructive lesion of bone. These abscesses were present as follows: a 3 cm. abscess on the dorsal surface of the left forearm over the distal end of the shaft of the radius; a 5 cm. abscess over the middle third of the right side of the clavicle, the adjacent first and second ribs and the

manubrium; a 2 cm. abscess over the costochondral junction of the right third rib; an 8 cm. abscess over the left fifth and sixth ribs in the anterior axillary line; a 3 cm. abscess over the acromion process of the right scapula; a 2 cm. abscess over the inferior angle of the left scapula; a 10 cm. abscess over the anterior superior spine and anterior 8 cm. of the crest of the right ilium; an 11 cm. abscess anteriorly over the spine and crest of the left ilium communicating with a 16 cm. abscess posteriorly involving the left sacroiliac joint; a 4 cm. abscess (without a draining sinus) located in the suprasternal notch which extended posteriorly and inferiorly around the left side of the trachea and had its origin from the first, second and third dorsal vertebrae.

The bone lesions varied from superficial periosteal and cortical erosions to extensive destructive lesions such as were present in the clavicle and the vertebral bodies. They resembled destructive tuberculous lesions.

The right lung weighed 740 Gm. and the left 625 Gm. Single and conglomerate yellowish gray nodules, measuring from 0.2 to 0.5 cm. in diameter, were scattered throughout both lungs. The upper lobes showed the greatest number. The intervening lung tissue was somewhat edematous but not consolidated. The peribronchial, hilar and mediastinal lymph nodes varied in size from 1.0 to 3.0 cm. and showed rubbery yellowish areas of necrosis from 0.2 to 1.0 cm. in diameter.

The right kidney weighed 175 Gm. and the left 155 Gm. Their capsules stripped readily, leaving a smooth surface except for several yellowish gray, slightly protruding small soft nodules in the cortex. There were no lesions in the pyramids or the pelves.

The subdural space was free of adhesions. A yellowish gray thin fibrinous exudate was present in the leptomeninx over the left temporal lobe. No nodules were associated with this exudate. Coronal sections after fixation revealed a 1.0 cm. abscess filled with a yellowish gray viscid purulent material located posteriorly to the tip of the left temporal lobe, adjacent to the sylvian fissure. The abscess apparently originated in the leptomeninx of a sulcus and involved the surrounding cortex secondarily.

The heart, liver, pancreas, adrenal glands, thyroid gland, gastrointestinal tract, spleen, urinary bladder, prostate, seminal vesicles and testes were free of granulomatous or suppurative lesions, and no important changes were noted in these organs.

Microscopic Examination.—The fundamental lesions in the lung consisted of interstitial tubercle-like foci, either single or conglomerate, with secondary involvement of the alveolar sacs. There was considerable variation in the cytologic composition of these lesions. One type, apparently a proliferative lesion, consisted of a miliary focus of epithelioid cells surrounded by a zone of lymphocytes, plasma cells and macrophages. Many of these lesions contained multinucleated giant cells, which were located in any portion of the lesion but had a tendency to lie toward a central location. The majority of the spherules in these lesions were located within giant cells, although some were also free within the tissue. Considerable variation in the number of these spherules was noted. Caseation was not present. The second type was primarily an exudative lesion. This was the predominate type. These lesions consisted basically of a central area of liquefactive necrosis, infiltrated by many polymorphonuclear leukocytes, with a variable quantity of surrounding epithelioid cell reaction, which gave some the appearance of a tubercle with central necrosis and others the appearance of a miliary abscess. In a few of these the necrosis was suggestive of caseation.

Partially disintegrated giant cells were not infrequently noted in these lesions. The spherules were more commonly found free in the tissue than phagocytosed, and small, apparently recently liberated spores were frequently observed. In addition to the interstitial lesions there were intra-alveolar lesions. These were similarly exudative lesions and often could be demonstrated arising directly from the interstitial tissues of the alveolar walls. In some areas considerable organization of the alveolar exudate was present. Fibrinous exudate was noted on the pleura over subpleural lesions. The hilar lymph nodes contained two general types of lesions, the first being primarily a proliferative type of tubercle-like lesion, similar to that noted in the lung, with varying quantities of connective tissue proliferation at its periphery. The second type of lesion consisted of a 1 to 4 mm. area of caseous necrosis surrounded by a rather dense hyalinized connective tissue wall. A few recently formed "tubercles" were noted extending into the adjacent tissues. Scattered, well preserved spherules were present in the connective tissue wall, and numerous pale ghost spherules, often showing only a rim of capsular substance, were present in the central necrotic tissue (fig., *A*).

The liver cells showed a moderate degree of degeneration. Numerous small foci of coagulative necrosis, surrounded by epithelioid cells, lymphocytes and connective tissue, were scattered throughout the parenchyma. Some of these contained a giant cell in the center of the lesion. Most of the lesions were located in the midzonal region. Spherules were noted in some of the lesions.

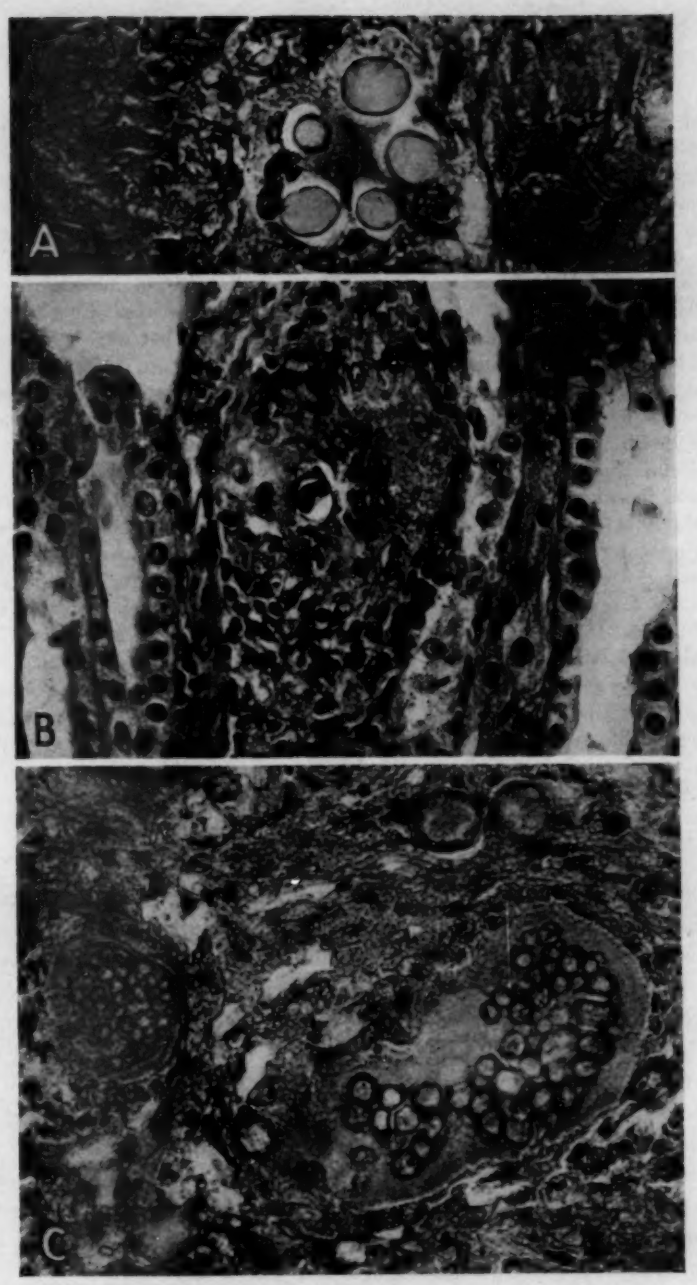
Several foci were present in the interstitial tissues of the renal cortex. The lesions were about the size of a glomerulus and consisted of a central area of necrosis associated with a few macrophages and polymorphonuclear leukocytes, the entire lesion being surrounded by lymphocytes. Once a single spherule without endosporulation was observed in the center of a necrotic area (fig., *B*). We failed to obtain a section of any of the larger lesions which were observed grossly.

A section from the first thoracic vertebra showed extensive necrosis of bone and infiltration by all the types of inflammatory cells which were seen in other lesions, as well as colliquative, coagulative and caseous necrosis. The proliferative responses noted elsewhere were also present. The organisms were numerous, and many of the spherules were enormous. Although the majority measured from 25 to 75 microns, many were much larger (fig., *C*), the largest measuring 262 microns in its over-all diameter with a 21 micron capsule; the endospores varied in size from 11 to 38 microns.

A section of muscle taken from the wall of an abscess over the crest of the ilium showed an inner zone of necrosis containing numerous polymorphonuclear leukocytes and cellular debris. Adjacent to this there was a zone composed chiefly of plasma cells, epithelioid cells, lymphocytes and a moderate number of giant cells. This gradually merged into an outer zone of fibrous tissue and skeletal muscle. Numerous spherules were present within the middle zone. Most of them lay free, although a few had been engulfed by giant cells. A few similar tiny foci were scattered throughout the skeletal muscle.

No specific lesions were present in the gastrointestinal tract, adrenal glands, thyroid gland, testes, seminal vesicles or prostate. No sections of spleen or brain were obtained.

Bacteriologic Study.—Coccidioides immitis was isolated in pure culture from the pus of a subcutaneous abscess in the thoracic wall March 3. Three blood cultures were made prior to death, and none revealed growth, the last being made about one week before death. At necropsy, cultures of the heart's blood, vertebrae, lungs and a subcutaneous abscess were made, and the organism was



A, photomicrograph of a section of a hilar lymph node, showing ghost spherules in the center of scar tissue. Hematoxylin and eosin stain; × 540.

B, photomicrograph of an interstitial lesion in renal cortex showing a single spherule, coagulative necrosis and cellular infiltration. This lesion is probably about one week old. Hematoxylin and eosin stain; × 420.

C, photomicrograph of a necrotic area in a thoracic vertebra, showing "giant" and average size spherules. Note the rupture of the capsule preceding the liberation of endospores into surrounding tissue. Hematoxylin and eosin stain; × 540.

isolated from each of these locations. It grew readily at 37 C., and colonies appeared in twenty-four to forty-eight hours. Growth occurred on plain broth, plain agar, brain broth, brain agar, blood agar and Sabouraud's medium. It failed to ferment dextrose, sucrose, lactose, maltose, mannite and inulin. On solid medium there was a white fluffy mesh of aerial hyphae with a firm attachment to the medium because of downgrowth during the first five to six days, after which a brownish color developed in the hyphae. A smear of the growth during the first few days showed branching septate mycelial threads. Chlamydospores appeared in some cultures during the first week of growth but were not uniformly present in all cultures until the second week.

The pus aspirated from a subcutaneous abscess was inoculated subcutaneously into groins of guinea pigs. An abscess developed at the site of inoculation, and soft yellowish lesions similar to tuberculosis in the regional lymph nodes, lungs and spleen. The animals lived an average of five weeks after inoculation. Intraperitoneal inoculation of guinea pigs with pus caused death in about four weeks. Yellowish tubercle-like lesions were found on the peritoneum and mesentery, and in the mesenteric lymph nodes, lungs and spleen. Male guinea pigs were not used, and hence the characteristic orchitis was not demonstrated. Rabbits were also inoculated with cultures of the organisms in the same manner and similar lesions produced. Rabbits inoculated intravenously with culture material died in two weeks and showed numerous miliary lesions in the lungs, liver, kidneys and spleen. The organism was readily recovered in pure culture from the lesions in the animals. Smears and tissue sections from these lesions showed organisms indistinguishable from those in the human tissues. A few failures, undoubtedly due to the use of freshly isolated cultures in which chlamydospores had not formed,[1] were encountered in the animal pathogenicity tests.

COMMENT

The similarity between the tissue reaction to the tubercule bacillus and that to Coccidioides immitis was quite striking in some respects. The proliferative response of the latter was not unlike that seen in primary tuberculosis, and the exudative reaction was not unlike that observed in the allergic reactions of reinfection tuberculosis or in overwhelming tuberculous infections. This feature was observed most prominently in the lungs.

The subcutaneous abscesses were of interest in that each one was associated with a lesion in bone, and it was our impression in each instance that the lesion in bone was the primary one. This is not the impression obtained from the literature regarding the pathogenesis of coccidioidal subcutaneous abscesses since in most of the reported cases none of the abscesses had a communication with a bone lesion.

The size of the organisms observed in pus, walls of abscesses, the lungs, hilar lymph nodes, the liver and the kidneys, showed the usual reported variations of from 10 to 70 microns. In the lesions of the vertebrae, however, giant spherules were present, the largest of which measured 262 microns through its greatest diameter. These contained spores varying in size from 11 to 38 microns. They also had a nonrefractile capsular substance which had the homogeneous pink-

staining appearance of chitinous substance. This capsule was as much as 21 microns thick. With Van Gieson's stain it was light brown, and with Cajal's trichrome stain it was light yellow.

The isolation of the organism post mortem from the cardiac blood is apparently an unusual experience. This was of particular interest since a negative blood culture was obtained one week before death, and indicates that systemic reinvasion probably occurred some time during the last few days of life. The small size of the renal and hepatic lesions seems to indicate that some at least were the result of this terminal invasion. This permitted an opportunity to study a lesion which was probably less than a week old and which contained only one spherule.

Some authors have expressed the view that the appearance of the disease in states other than California is explained by the spread of the disease through the medium of migratory patients. Others believe it possible that there are other endemic foci which may account for these cases. An analysis of the geographic distribution of the cases (table) tends to shed some light on this subject. Only 27 cases (including the authors') have been reported outside of California in the twenty-nine years that the disease has been known to occur elsewhere [15] in the United States. During this same period a large number have been observed in California. Excluding those cases with a California contact (cases 5, 6, 10 and 24 to 27), the case with the laboratory infection (case 9), the case with the Nicaragua contact (case 12) and the case of the World War I veteran, whose contacts were unknown (case 19), we have remaining only 17 cases in which the origin was outside of California. The source of infection in 12 (70.5 per cent) of these was probably in Texas, Arizona or New Mexico. Thus in only 5 cases (cases 2, 3, 4, 7 and 11) was the source of infection traceable to states other than California, Texas, Arizona or New Mexico. It seems probable that a proper survey of selected areas in the Southwest would reveal other endemic foci besides the California focus. The results of three different surveys recently reported by Mills and Farness [16] indicate that an endemic focus exists in Arizona. Intradermal coccidioidin tests were made on 60 citizens of Arizona by Farness, and 20 per cent had positive reactions. C. A. Thomas conducted another survey in Tucson, Ariz., on 60 patients, most of whom were non-Arizonians, and found that 10 per cent had positive skin reactions to coccidioidin. The third survey was conducted by Aronson, who tested 141 school children at the Pima Indian Agency and found that 90 per cent had positive skin reactions. The fact that man to man transmission of the disease has

15. (*a*) MacNeal, W. J., and Hjelm, C. E.: J. A. M. A. **61**:2044, 1913. (*b*) Morris, R. T.: ibid. **61**:2043, 1913.

16. Mills, C. W., and Farness, O. J.: Tr. Am. Clin. & Climat. A. **56**:147, 1941.

not been observed is further support of the view that local factors are responsible for the appearance of the disease rather than itinerant patients.

SUMMARY

A case of coccidioidomycosis of the granulomatous type is reported from Louisiana. The patient was probably infected as a result of handling fruit in California. The features of particular interest were: (1) proliferative and exudative lesions simulating the reactions in primary and reinfection tuberculosis; (2) subcutaneous abscesses all of which had their origin in bone; (3) giant spherules measuring as much as 262 microns in diameter; (4) systemic reinvasion of the blood stream during the last week of life; (5) renal lesions of probably less than one week's duration.

A geographic survey of the reported cases outside of California indicates that the disease is probably not spreading directly to persons in other states through the medium of migratory patients. An endemic focus is apparently present in Arizona, and it is suggested that there may be other endemic foci in the Southwest.

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METASTATIC TUMORS OF THE NERVOUS SYSTEM

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Tumor metastases in the nervous system are not unusual, and numerous reports dealing with them have accumulated within the medical literature. It seemed opportune to review this subject so that one may determine how much information is still lacking from knowledge of these lesions. In order to complete such a study and to verify some of the statements now present in the literature, it was believed advantageous to undertake also a detailed analysis of observations recorded in the files of the division of nervous and mental diseases at the University of Minnesota on 114 tumors that were proved to be metastatic to the nervous system. Ninety-two of these were studied pathologically.

FREQUENCY

There exists some difference of opinion as to the frequency of tumor metastases in the nervous system. The figures reported have naturally varied, depending on the location of the primary growth, the thoroughness of the pathologic studies and the frequency with which autopsy studies have been performed. Since encephalic lesions are often not suspected and the central nervous system not examined, the figures reported are probably underestimates of the actual incidence. Krasting [1] drew attention to the fact that the brain for some reason favored the localization of metastases. In his series of 935 verified cases of cancer in which the brain was studied, there were 53, or 5.6 per cent, in which the brain contained metastases. Rau [2] reported 28, or 3.2 per cent, intracranial metastases in a series of 851 autopsies in cases of cancer. Grant [3] and Willis [4] reported 4 and 4.5 per cent of such metastases in their cases, respectively. One of the highest figures was reported by Romay,[5] who observed 7 per cent intracranial involvement in 286 cases.

From the Division of Nervous and Mental Diseases, University of Minnesota.

This study was aided by a grant from the University of Minnesota Graduate School and by the Work Projects Administration, Official Project no. 165-1-71-124, Subproject no. 360.

1. Krasting, K.: Ztschr. f. Krebsforsch. **4**:315, 1906.
2. Rau, W.: Ztschr. f. Krebsforsch. **18**:141, 1921.
3. Grant, C. F.: Ann. Surg. **84**:635, 1926.
4. Willis, R. S.: The Spread of Tumors in the Human Body, London, J. & A. Churchill, 1934.
5. Romay, R. S.: Arch. argent. de neurol. **20**:89, 1939.

If one compares the figures for frequency of encephalic metastases from the individual primary foci, the incidence becomes much more varied, indicating a definite tendency for tumors of certain organs to select the brain as a site of distant involvement. Probably the two most common primary sources for intracranial metastases are cancer of the lungs and melanoma of the skin. The statistics on the latter vary from 8.7 per cent, reported by Paillas,[6] to 50 per cent, by Courville and Schillinger.[7] The reported frequency of intracranial metastases from primary cancer of the lung varies from a low of 4.2 per cent (Brunner [8]) to a high of 39.2 per cent (Fried and Buckley [9]). Other reports list the following frequencies: Dosquet,[10] 31 per cent; Simpson,[11] 13.7 per cent; Davison and Horwitz,[12] 19 per cent. Large series of tumors metastasizing to the nervous system from other primary sources are not numerous. Lenz and Freid [13] observed metastases in the central nervous system in 15 per cent of 168 cases of carcinoma of the breast, while Krasting [1] reported 18 per cent. This same author observed encephalic metastases in 22.2 per cent of cases of primary carcinoma of the uterus.

Because of the great interest created by the newer histologic classification of primary tumors of the brain, the relative importance and frequency of the metastatic lesions have failed to receive their proper emphasis and attention. This is especially true in large surgical clinics, where the great reluctance to operate on patients for metastatic tumor would naturally reduce the verified frequency of these lesions. It is for this reason, no doubt, that Meagher and Eisenhardt [14] and Cushing [15] reported such low figures as 3 and 3.2 per cent metastatic tumors, respectively, in their predominantly surgical series of intracranial neoplasms. Elkington,[16] in studies of records of the National Hospital, Queens Square, London, found that of 805 histologically verified brain tumors, 72, or 9 per cent, were metastases. He expressed the opinion

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6. Paillas, J., cited by Roger, H., and Paillas, J. E.: Presse méd. **42**:2093, 1934.

7. Courville, C. B., and Schillinger, R. J.: Bull. Los Angeles Neurol. Soc. **4**:8, 1939.

8. Brunner, W.: Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:793, 1936.

9. Fried, B. M., and Buckley, R. C.: Arch. Path. **9**:483, 1930.

10. Dosquet, H.: Virchows Arch. f. path. Anat. **234**:481, 1921.

11. Simpson, S. L.: Quart. J. Med. **22**:413, 1929.

12. Davison, C., and Horwitz, W. A.: Arch. Int. Med. **46**:680, 1930.

13. Lenz, M., and Freid, J. R.: Ann. Surg. **93**:278, 1931.

14. Meagher, R., and Eisenhardt, L.: Ann. Surg. **93**:132, 1931.

15. Cushing, H.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

16. Elkington, J. St. C.: Proc. Roy. Soc. Med. **28**:1080, 1935.

that his figures were probably too low and that metastatic lesions probably comprise as high as 20 per cent of all brain tumors. Garland and Armitage [17] in 264 autopsies on persons with brain tumors at the General Infirmary in Leeds, England, observed that the tumors were metastatic in 12.8 per cent of the cases. Roger and Paillas [18] at the Neurological Institute in Marseilles, France, found 10 per cent of all brain tumors were metastases. Other reports are those of: Gagel,[19] 6 per cent; Hare and Schwarz,[20] 10 to 20 per cent; Carmichael,[21] 9.3 per cent; Davidoff and Ferraro,[22] 2.6 per cent.

Most of the statistical studies reported contain definite defects which make the evaluation of the data somewhat difficult. For example, many have been restricted to neurologic institutions, where naturally the patients have symptoms and signs of involvement of the nervous system. Figures from such studies cannot be considered as giving the true picture since many brain metastases produce no obvious neurologic symptoms or else the symptoms of the primary neoplasm completely overshadow those from the metastases, which are therefore overlooked clinically. More accurate statistics would be obtained from a general hospital where routine autopsy studies are performed. Even the figures from such an institution would be far too low, since the brain is usually not examined routinely unless the indications are obvious. Often when the skull is opened and the contents examined, many metastases are overlooked because they are too small to be easily detected on gross examination.

I cannot claim greater accuracy for my own statistics since they have been accumulated from routine autopsy studies of the department of pathology at the University of Minnesota. Here, too, there would be a tendency to make studies of the brain only in those cases in which neurologic symptoms were obvious, so that many cases of intracranial metastasis, no doubt, were overlooked. In some of the cases, in spite of the clinical evidence of encephalic involvement, the brain was not examined either because of a failure to obtain permission for such a study or because the primary lesion so overshadowed the picture that the neurologic symptoms were overlooked. Therefore, my associates and I carefully reviewed the clinical records of all primary tumors in the study of which no examination of the head was made and selected those cases in which there appeared to have been clinical evidence of an involvement of the nervous system. These cases were then added to the

17. Garland, H. G., and Armitage, G.: J. Path. & Bact. **37**:461, 1933.
18. Roger, H., and Paillas, J. E.: Rev. neurol. **69**:730, 1938.
19. Gagel, O.: Ztschr. f. d. ges. Neurol. u. Psychiat. **161**:69, 1938.
20. Hare, C. C., and Schwarz, G. A.: Arch. Int. Med. **64**:542, 1939.
21. Carmichael, E. A.: J. Path. & Bact. **31**:493, 1928.
22. Davidoff, L. M., and Ferraro, A.: Am. J. Psychiat. **8**:599, 1929.

ones in which the presence of such metastases had been pathologically proved, in order to convey a little more accurately the frequency of encephalic metastases from each of the various primary sources. The figures are listed in table 1. The relative frequency of the metastatic tumors among all intracranial neoplasms in this series of cases is given in table 2.

SPREAD OF METASTASES

The manner in which metastases reach the central nervous system is subject to much difference of opinion, although most investigators at

TABLE 1.—*Frequency of Metastases from Different Primary Sources*

Primary Site of Neoplasm	Cases	Cases with Intracranial Metastases: Proved at Autopsy	Cases with Intracranial Metastases: Indicated Clinically but Not Proved at Autopsy	Cases with Intracranial Metastases: Total	Cases with Questionable Symptoms of Brain Involvement	Cases with No Clinical Evidence of Involvement of the Brain
Lung	267	24	10	34 (12.5%)	15	218
Breast	241	24	15	39 (16.1%)	15	187
Stomach	901	4	26	30 (3.3%)	36	835
Prostate	272	1	11	12 (4.3%)	11	249

TABLE 2.—*Classification of Intracranial Tumors Based on Six Hundred and Thirty-Seven Microscopically Verified Cases Submitted to the Department of Pathology, University of Minnesota*

I.	Tumors of nerves	8
II.	Tumors of meninges	96
III.	Glioma	306
IV.	Vascular tumors	29
V.	Tumors of mixed tissues	6
VI.	Hypophysial tumors	36
VII.	Granuloma	30
VIII.	Miscellaneous group	12
IX.	Metastatic tumors	114 (17.9%)

the present time favor the hematogenous route. However, there is still a group who believe that at least the meningeal metastases can result from invasion of the subarachnoid space through the perineural or perivascular lymphatics.

Lymphatic Spread.—Rehm,[23] Knierim,[24] Maass,[25] Miller,[26] Cornwall [27] and Miskolczy [28] all expressed the belief that the metastatic tumor

23. Rehn, E.: Virchows Arch. f. path. Anat. **186**:307, 1906.
24. Knierim, G.: Beitr. z. path. Anat. u. z. allg. Path. **44**:409, 1908.
25. Maass, S.: Arch. f. Psychiat. **51**:359, 1913.
26. Miller, J. W.: Centralbl. f. allg. Path. u. path. Anat. **28**:161, 1917.
27. Cornwall, L. H.: Arch. Neurol. & Psychiat. **17**:466, 1927.
28. Miskolczy, D.: Arch. f. Psychiat. **90**:268, 1930.

cells spread from the primary intra-abdominal or intrathoracic neoplasm to the regional lymph nodes, which are frequently found to be full of the neoplastic elements. From here they spread through the lymph channels of the peritoneum to reach the lymph spaces around the lumbar and the sacral plexus. They then pass with the nerves through the intervertebral foramens into the spinal canal. Here they penetrate into the endoneurium to reach the spaces between the nerve fibers and in this manner reach the spinal rootlets. They then pass with the rootlets into the subarachnoid space and spread diffusely through this space, reaching even to the cerebral hemispheres, where they may extend with the vessels into the brain substance. Willis [4] suggested that to substantiate such a mode of spread it would be necessary to demonstrate three very important features, namely:

1. That extensions of the primary growth were present around the peripheral nerves or vessels up to their entry at the bony foramens.
2. That the vessels or nerve rootlets within the spinal canal exhibited neoplastic involvement.
3. That secondary growths in the brain or the spinal cord (from which meningeal extension could arise) were absent or, if present, were unlikely to yield such a spread.

Most investigators advocating such a spread have been unable to fulfil these three requirements in their cases. Usually they have failed to demonstrate actual involvement of nerve roots within the spinal canal. The only completely studied case that could be accepted as supporting a possible lymphatic spread was reported by Knierim,[24] the case of a 57 year old man with carcinoma of the stomach. The author demonstrated tumor cells within the peritoneal lymph spaces, the lymph spaces around the sacral nerves, around the spinal ganglions and around the nerve rootlets and finally throughout the spinal canal.

A second method of lymphatic spread was advocated by Hassin.[29] He expressed the belief that cells from a primary tumor within the chest or the neck may spread through the lymph channels to the lymph glands of the neck. From here they extend through the tissue spaces to the so-called perineural spaces around some of the cranial nerves, chiefly the fifth, tenth and twelfth, to reach finally the subdural and subarachnoid spaces, where they result in meningeal metastases. To substantiate this explanation of tumor spread, Hassin showed that a substance such as Richardson blue or prussian blue when injected into the subdural space easily reaches the lymph glands of the neck. However, in order to accept such a hypothesis one would have to assume that the tumor cells once

29. Hassin, G. B.: Arch. Neurol. & Psychiat. 1:705, 1919.

reaching the tissue spaces of the neck are capable of traveling against the current to reach the subarachnoid space. It is a little difficult to accept such a retrograde flow of the lymph current from the neck to the brain. If such a flow did occur, one would certainly expect carcinoma of the tongue or of the face to give rise to meningeal involvement frequently, but this is not the case.

Hematogenous Spread.—There are numerous factors that tend to suggest that the hematogenous mode of spread is the most likely one.

1. The frequency of vascular involvement within the primary neoplasm. Goldmann [30] described these changes in great detail. In his opinion the most extensive involvement occurred within the veins. The changes consisted of: (*a*) thrombosis of the veins by tumor cells, (*b*) intramural invasion of the vessel walls, producing endothelial proliferation with narrowing of the lumens and (*c*) direct invasion of the venous wall by the tumor cells with complete replacement and weakening of the walls and secondary hemorrhage. Siefert,[31] in a study on choriocarcinoma, described the cells of the primary cancer consistently filling the blood vessels to form tumor thrombi and tumor emboli.

2. The greater frequency of intracranial metastases from pulmonary cancer. If the spread of carcinoma cells is through the blood stream, one would expect pulmonary cancer to produce intracranial metastases the most frequently, since involvement of the pulmonary veins within the primary neoplasm would lead to a spread directly into the left side of the heart and hence into the systemic circulation. A similar tumor embolus from any other organ would first have to pass through the lung capillaries before reaching the brain and in many cases would probably be retained within the lungs, which act as a barrier to such emboli.

3. Histologic intracranial vascular involvement by tumor cells. Careful histologic examination of the brain in cases of cancer will occasionally reveal vascular involvement in the absence of any gross tumor nodules. The neoplastic cells fill the small cerebral arteries and occasionally invade and destroy the vessel walls. Such small lesions are frequently overlooked on casual study (see section on microscopic pathology).

4. The infarction of the brain produced by tumor emboli. Busse,[32] Thompson and Evans [33] and Storjohann [34] described infarction of the brain caused by tumor emboli occluding some of the larger cerebral

30. Goldmann, E. E.: Beitr. z. klin. Chir. **72**:1, 1911; **18**:595, 1897.
31. Siefert, E.: Arch. f. Psychiat. **38**:1, 1904.
32. Busse, O.: Virchows Arch. f. path. Anat. **174**:207, 1903.
33. Thompson, T., and Evans, W.: Quart. J. Med. **23**:135, 1929.
34. Storjohann, K. R.: Frankfurt. Ztschr. f. Path. **43**:80, 1932.

vessels. These authors were unable to find any indication of tumor involvement within the softened areas save for the vascular emboli.

5. The distribution of metastases in the brain. Gallavardin and Varay,[35] Fried,[36] Miller [26] and Rich [37] all commented on the fact that the metastases seem to occur predominantly within the gray substance or within the subcortical white matter, where the blood supply is most abundant. Courville and Schillinger,[7] in a study of 18 cases of melanoma with intracranial metastases, noticed the localization of these lesions about the sylvian fissure, within the cortex, subcortex and basal ganglions, in those areas supplied by the middle cerebral artery. They intimated that the spread, therefore, was chiefly hematogenous.

6. The common occurrence of metastases within the choroid plexus. Such metastases have been reported by numerous investigators.[38] The frequent involvement of this structure certainly lends support to the probable blood-borne character of this metastatic process.

7. The presence of tumor cells within the blood stream. Such observations probably offer the greatest substantiation of the belief that the spread is hematogenous. The demonstration of tumor emboli in the circulating blood has been claimed by Quensel,[39] who observed cancer cells circulating in the blood in 6 of 50 cases that he studied. He obtained the blood from the right auricle at necropsy.

The tumor cells reach the blood stream through the invasion of the vessels within or adjacent to the primary neoplasm. They penetrate the veins and produce thrombosis or endophlebitis. If the smaller vessels are involved, there may result speedy occlusion with no dissemination into the blood stream. It is when a larger vessel is invaded that there occurs only partial obliteration of the lumen and hence prolific liberation of tumor emboli. These emboli may consist of single cells, clumps of cells or fragments of tumor thrombi composed of tumor cells clothed by thrombus material, namely, fibrin, red cells, leukocytes and platelets. Even when the tumor cells spread originally through the lymphatic system, they eventually reach the nervous system through the thoracic

35. Gallavardin, L., and Varay, F.: Rev. de méd., Paris **23**:441, 1903.

36. Fried, B. M.: Arch. Int. Med. **35**:1, 1925.

37. Rich, G. J.: Arch. Neurol. & Psychiat. **23**:742, 1930.

38. (*a*) Pilcz, A.: Centralbl. f. allg. Path. u. path. Anat. **14**:50, 1903. (*b*) Langhans, T.: Virchows Arch. f. path. Anat. **189**:69, 1907. (*c*) Ginsberg, S.: Klin. Monatsbl. f. Augenh. **67**:232, 1921. (*d*) Weller, C. V.: J. Cancer Research **7**:313, 1922. (*e*) Foot, N. C.; Carter, B. N., and Flipse, M. J.: Am. J. M. Sc. **167**:76, 1924. (*f*) de Biasi, W.: Virchows Arch. f. path. Anat. **261**:885, 1926. (*g*) Danisch, F., and Nedelmann, E.: ibid. **268**:492, 1928. (*h*) Putschar, W.: Ztschr. f. d. ges. Neurol. u. Psychiat. **126**:129, 1930.

39. Quensel, U.: Upsala läkaref. förh. **26**:1457, 1921; abstracted, J. A. M. A. **77**:1613, 1921.

duct, the right lymphatic duct or their tributaries. From the venous circulation the tumor emboli, in order to reach the brain, must pass through the lungs. The smaller ones may occasionally pass directly through the wide pulmonary capillaries to the left side of the heart without stopping. Tumor emboli too large to traverse these small vessels suffer arrest within the lungs. Here they may start growing to produce gross pulmonary lesions and later may break through into the pulmonary vein and the left side of the heart to produce metastases in the brain. Occasionally the neoplastic cells remain caught within the small pulmonary vessels and produce carcinomatous endophlebitis. From such a lesion isolated or clumped cells may then break off and pass through the lung capillaries into the left side of the heart. These small pulmonary lesions are often not detected on gross inspection and are even overlooked on cursory microscopic studies. Schmidt,[40] in examining 41 cases of carcinoma for pulmonary metastases, found in 15 evidence of involvement only on careful microscopic study. The lesions in each case consisted either of a group of cancer cells caught within a blood vessel or of small tumor nodules that had produced endophlebitis. In none of these cases had the neoplastic process extended outside the vessel to involve the adjacent tissues.

Once through the pulmonary circulation, the tumor cells can easily reach and become disseminated throughout the brain, where many neoplastic emboli perish or remain static and hence do not produce progressive lesions. Only if the transported cells survive, multiply and attain an extravascular spread does there result a metastatic tumor.

In those cases of blood-borne metastases in the brain without visible pulmonary involvement, one is faced with the problem of explaining how the tumor cells passed through the pulmonary circulation. Numerous explanations may be suggested for such an occurrence.

1. Small tumor emboli may pass directly through the wide capillaries of the lungs to the left side of the heart without being retained within the lungs. These emboli no doubt consist of isolated cancer cells or very small clumps which are small enough to be carried through such vessels. However, since most tumor emboli probably consist of clumps of cells or actual pieces of tumor thrombi, the greater majority would be arrested within the smaller pulmonary vessels.

2. Pulmonary lesions may actually be present but so small that they are overlooked on gross and even on microscopic examination. The tumor emboli arrested within the smaller pulmonary vessels set up

40. Schmidt, M. B.: Die Verbreitungswege der Karcinome, und die Beziehung generalisierter Sarkome zu den leukämischen Neubildungen, Jena, Gustav Fischer, 1903.

carcinomatous endophlebitis. Single cells may then break off from this vascular thrombus to reach the left side of the heart.

3. Paradoxic embolism might occur. Here the tumor emboli avoid the pulmonary system by passing from the right side of the heart to the left side through a patent foramen ovale. In few cases has metastasis actually resulted through this pathway, and paradoxic emboli probably play an infrequent part in the dissemination of tumors. Thompson and Evans [33] made a careful review of this subject and reported a case which could be accepted as fulfilling the necessary requirements. Their patient, a 25 year old man, died from teratoma of the testis. At autopsy the foramen ovale was patent, and a tumor growth attached to the right surface of the interauricular septum extended through the patent foramen ovale into the left side of the heart. Fragments of tumor tissue were found in the left ventricle, and a tumor thrombus obstructed the middle cerebral artery.

4. Finally, Batson [41] suggested a retrograde blood flow as a means of producing metastases in the brain without involving the lungs. He expressed the belief that the entire system of epidural and vertebral veins has at each spinal segment a rich anastomosis with veins of the thoracicoabdominal cavity. The pressure within these veins is low. With every compression of the trunk such as occurs in straining, lifting or coughing, the intratruncal pressure would be raised sufficiently to produce a blood flow not into the vena cava but backward into the vertebral venous system. Tumor cells could then be driven from the abdominal veins into the vertebral veins and then into the intracranial cavity without going through the lungs. To verify this mode of spread, Batson,[41] using cadavers, injected a radiopaque substance into the dorsal vein of the penis and was able to follow the dye upward through the vertebral veins into the intracranial cavity. He also injected the dye into the small vein of the breast. The dye passed into the intercostal veins and then into the cranial venous sinuses.

CLINICAL OBSERVATIONS

General Considerations.—A review of the clinical findings in all of the cases of intracranial metastases included in this study is impossible since in 17 per cent the histories of the illness and the neurologic findings were somewhat incomplete. However, enough of the patients were studied carefully to allow a fairly adequate consideration from the point of view of symptomatology. It must be realized that estimates of the frequency of certain symptoms and signs will probably be understatements.

41. Batson, O. V.: Ann. Surg. **112**:138, 1940.

Before beginning a discussion of the symptoms, it might be helpful to analyze the cases as to the locations of the primary neoplasms, the ages at death of the patients relative to their primary neoplasms, the locations of the metastases within the brain and finally the relative frequency of the various encephalic symptoms and signs. These factors often prove helpful in the final clinical evaluation of the case.

(*a*) Locations of the Primary Neoplasms (table 3). The four most frequent sources of intracranial metastases were the lung, the breast, the gastrointestinal tract and the kidney. The figures in table 3 agree fairly

TABLE 3.—*Locations of Primary Neoplasms*

Location	Primary Neoplasms	Location	Primary Neoplasms
Lung	24	Eye	2
Breast	24	Liver	1
Skin	9	Thyroid	1
Kidney	9	Bone	1
Adrenal	6	Antrum	1
Colon	6	Prostate	1
Stomach	4	Gum	1
Pancreas	4	Esophagus	1
Testis	3	Turbinate	1
Uterus	5	Tonsil	1
Urinary bladder	2	Ovary	1
Rectum	2	Undetermined	4

TABLE 4.—*Ages of Patients at Time of Death*

Site of Primary Neoplasm	Cases	Age of Youngest Patient, Yr.	Age of Oldest Patient, Yr.	Average Age, Yr.
Lung	24	33	61	48
Breast	24	37	79	53
Gastrointestinal	12	31	79	53
Skin	9	25	80	56
Kidney	9	39	73	54
Adrenal	6	2½	59	26

closely with those already quoted in the literature, although metastases from cancer of the breast were somewhat more frequent than is usually reported. When one attempts to determine how many tumors of a certain organ will metastasize to the brain, one engages in a fairly formidable task. Such an attempt was made for certain primary tumors by reviewing all the case histories. A tabulation of the findings is given in table 1.

(*b*) Ages of Patients at Time of Death. The ages of the patients in the present series at the time of death relative to their primary neoplasms are of interest because it aids in establishing the most susceptible age groups (table 4). It appears from this table that metastasis to the nervous system from tumors of different organs occurs most frequently

between the fifth and the seventh decade of life, primarily in the sixth decade. Metastasis from adrenal tumors is an exception, primarily because certain types of adrenal tumors characteristically occur in children and hence reduce the general average age. It is interesting to note, and very important to keep in mind, that certain patients may die of intracranial metastases before the end of the fourth decade of life. These patients, because of their age, are often not suspected of harboring such lesions and receive an incorrect diagnosis.

TABLE 5.—*Locations of Metastases in the Central Nervous System*

Location	Frequency of Involvement	Location	Frequency of Involvement
Parietal lobe	38	Pons and medulla	10
Meninges	31	Basal ganglions	8
Cerebellum	27	Spinal cord	5
Frontal lobe	20	Lateral ventricle	4
Occipital lobe	20	Midbrain	3
Unspecified	13	Third ventricle	3
Temporal lobe	10	Optic nerve	2

TABLE 6.—*Locations of Multiple and Single Metastases*

Region	Cases with Multiple Metastases	Cases with Single Metastases
Leptomeninges alone	4	0
Leptomeninges plus other structures	3	0
Dura alone	9	6
Dura plus other structures	4	0
All meninges	1	0
Cerebrum alone	17	18
Cerebellum alone	1	13
Cerebrum and cerebellum	13	0
Brain stem alone	3	0
Brain stem plus other structures	9	0
Cord	2	3
Spinal roots	1	0

(*c*) Locations of Metastases. The sites of the metastases in the central nervous system are tabulated in tables 5 and 6. In many cases the metastases were multiple and hence the cases were included under more than one location, although solitary metastases were not uncommon. The latter seem to occur frequently when the cerebellum alone is involved. In the cerebrum, single or multiple lesions occur with about equal frequency. Since the entire brain was not available in every case for detailed pathologic examination, it is very probable that many of the smaller lesions were overlooked and that the percentage of solitary metastases here stated is somewhat high.

Special Symptoms Referable to Involvement of Different Parts of the Nervous System.—It might be well to introduce this discussion of the clinical symptoms and signs with a tabulation of the findings in my cases

in the order of their frequency (table 7). Because of the variation in size, number and location of the metastases, the clinical picture is most variable and a diagnosis often difficult to make. If the presence of a primary tumor is known, metastases are suspected immediately at the very onset of any symptoms referable to the central nervous system. However, when the primary tumor remains symptomless and is discovered only after recognition of the nature of the neurologic involvement, the diagnosis often becomes difficult. Bailey [42] stated: "Primary pulmonary tumors in their early stages are difficult to recognize and may remain entirely symptomless until after the cerebral metastases are well developed. These pulmonary tumors are so numerous that any patient who develops symptoms of intracranial tumor rather rapidly in middle life or later should have a careful examination of the chest,

TABLE 7.—*Clinical Findings in Ninety-Seven Cases of Metastatic Tumor*

	Cases
1. Headaches	39
2. Mental symptoms (confusion, impairment of memory, change in personality, hallucinations)	37
3. Paresis	36
4. Nausea and vomiting	21
5. Generalized weakness	19
6. Vertigo	16
7. Convulsions	16
8. Pain and numbness of limbs	13
9. Speech defect	12
10. Coma, sudden	11
11. Paralysis	10
12. Lethargy	10
13. Visual disturbances (decrease, diplopia, nystagmus)	10
14. Choked disk	9
15. Stiff neck and positive Kernig sign	7
16. Anorexia	6
17. Periods of unconsciousness	5
18. Cranial nerve palsy	5

including a roentgenogram, whether pulmonary symptoms are present or not." One may broaden this statement by saying that any patient in whom symptoms of an intracranial tumor develop rather rapidly in middle life or later should have a careful investigation for a primary neoplasm somewhere in the body, with special attention being directed to the lungs, the breasts, the kidneys and the gastrointestinal tract, from which sources many of the intracranial metastases are derived.

Since metastases may involve the brain, the meninges, the cord or the peripheral nerves, alone or in any combination, the clinical picture naturally would depend on which structures are invaded. For the sake of simplicity, however, the clinical symptoms will be formulated as if each of these structures alone was involved.

42. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

(*a*) Brain. The onset of encephalic symptoms may be gradual or sudden. If the tumor embolus produces vascular occlusion and infarction of the brain, the onset simulates apoplexy. On the other hand, actual invasion by tumor cells requires that the neoplastic elements establish themselves and grow within the brain. For this reason the appearance of symptoms is usually more gradual and resembles the picture presented by a primary tumor of the brain. The actual symptoms fall into two categories: first, those symptoms and signs of increased intracranial pressure primarily due to simple mass growth of the metastases rather than to block of spinal fluid flow; second, focal symptoms and signs due to involvement of the function of the part of the brain encroached on by the neoplasm.

The symptoms and signs of increased intracranial pressure are well known and consist of headaches, nausea, vomiting, vertigo, diplopia, choked disks, failing vision and mental disturbances. Of these, the first four appear to be the most common in patients with intracranial metastases, headaches being present in 39 of the patients in my series. The records concerning choked disk in the cases reported here are probably inadequate. In only 8 cases was such a finding recorded. Papilledema would probably be reported much more frequently if careful and repeated ophthalmoscopic studies had always been performed. Dickson and Worster-Drought,[43] in their 14 cases of metastasis to the brain from tumor of the lung, reported papilledema occurring in all at some time during the course of the illness. Romay,[5] in his 20 cases of cerebral metastases, observed that most of the patients had some degree of choking of the disk. These figures are probably somewhat high since increased intracranial pressure does not always occur in the presence of metastases. In fact, its relatively uncommon appearance has been considered by many as one of the characteristic features of metastatic growths within the brain. This can be explained by the nature of the metastases. Pathologically, they are usually invasive, destructive lesions that replace rather than displace brain tissue.

Much more frequent than the signs and symptoms of increased intracranial pressure are the slowly progressive focal findings secondary to destruction of brain tissue. These consist of ataxia, monoplegia, hemiplegia, aphasia, generalized convulsions and jacksonian seizures. The patients may have mild indefinite headaches for a short period and then present any of the aforementioned focal findings without the appearance of any indications of increased intracranial pressure. Progressive weakness and paralysis of the limbs were the most common focal findings, occurring in 46 cases. Aphasia was associated with the paresis in 6

43. Dickson, W. E. C., and Worster-Drought, C.: J. Neurol. & Psychopath. **16**:289, 1936.

cases and was the presenting symptom in 1. The illness made its appearance with generalized convulsions in 5 cases and with jacksonian seizures in 2. After a few months the patients begin to undergo transient confusion and lethargy, which eventuates in stupor, coma and death. Occasionally, the patient without any premonitory symptoms suddenly becomes stuporous or comatose and dies in a few days or weeks. Four such cases occurred in the present series. If the primary neoplasm is known, the diagnosis is often suspected; otherwise, the patient's condition remains undiagnosed clinically and often is suspected of being due to a vascular accident.

Mental symptoms may occur alone or in conjunction with the other generalized or focal findings already discussed. Mental symptoms from intracranial metastases have already been reported by a number of authors.[44] Occasionally the mental symptoms are the most outstanding disturbance manifested by the patients. In such cases, the presence of a tumor of the brain may easily be overlooked and the illness classified as a primary psychogenic disorder. Thirty-seven of the patients in the present series showed some type of mental disturbance during the course of their illness.

In summary, therefore, the neurologic symptoms from intracranial metastases may appear as the symptoms of increased intracranial pressure, as focal symptoms secondary to damage of the brain or as mental disturbances. Any combination of these findings may be present. The clinical course is usually rapidly progressive, with the illness terminating after a relatively short time.

(*b*) Meninges. The presence of tumor cells within the subarachnoid space or within the meninges does not always result in clinical symptoms. Such an involvement frequently does, however, produce three groups of symptoms, namely, those of meningeal irritation, those of increased intracranial pressure due to the infiltration of the basal meninges and blockage of the arachnoidal cisterns and focal findings secondary to compression of the brain by a large metastatic meningeal tumor mass. The last two groups of symptoms have already been discussed under metastatic involvement of the brain. The clinical picture resulting from meningeal irritation is well known and consists of headaches, vomiting, stiff neck, pain in the neck, retraction of the head, Kernig's sign, jacksonian attacks and occasionally generalized convulsions. The only symptoms which are pathognomonic for meningeal irritation are the intense cervical pain referred to the back of the head and neck, stiffness of the neck and Kernig's sign. In 31 of the present cases there was

44. (*a*) Elzholz, A.: Jahrb. f. Psychiat. u. Neurol. **17**:144, 1898. (*b*) Miura, K.: Klin. Wchnschr. **37**:905, 1891. (*c*) Buchholz: Monatschr. f. Psychiat. u. Neurol. **4**:183, 1898. (*d*) Scanzoni, C.: Ztschr. f. Heilk. **13**:381, 1897. (*e*) Saenger, A.: Neurol. Centralbl. **19**:187, 1900.

definite meningeal involvement at autopsy; in 15 of these there was only dural involvement. In 5 cases the leptomeninges and the subarachnoid space alone were invaded by the neoplastic elements. In 4 of these the typical findings of meningeal irritation were exhibited as the presenting clinical symptoms. At the onset of the illness there appeared a mild but progressive headache associated with some dizziness, cervical pain and stiffness of the neck. After a short time the patients became somewhat drowsy and often began to manifest convulsive seizures. The course of the illness was usually very rapid. Terminally in these patients papilledema frequently developed.

Metastases in the brain, after increasing in size, may become implanted within the leptomeninges by rupturing through the cortex or the walls of the ventricles. In such cases the characteristic symptoms of meningeal involvement may be superimposed on the symptoms and signs produced by the encephalic lesion. Such a clinical sequence apparently occurred in 10 of the present cases.

(*c*) Spinal Cord. Intramedullary metastases are unusual and very few cases have been reported in the literature.[45] The symptoms referable to the spinal cord are usually due to changes within the cord secondary to the meningeal involvement. The symptoms produced by such changes would be similar to those caused by any type of extramedullary tumor and would be those of involvement of long nerve tracts of both motor and sensory type. Rarely an actual intramedullary metastasis occurs, producing a syringomyelic syndrome with dissociated sensibility as the outstanding feature. Such a syndrome was encountered in only 1 case of the present series. Extensive cord symptoms have been reported in the absence of actual neoplastic involvement (Siefert[31]; Lubarsch[46]). Lubarsch observed diffuse degeneration of the posterior and lateral columns of the spinal cord in 11 of 19 cases of carcinoma of different organs. The involvement appeared as acute myelitis. No actual tumor was found. It has been speculated that such lesions are caused by a toxin liberated by the primary neoplasm.

(*d*) Nerves and Nerve Roots. Nerve and radicular involvement in metastatic carcinoma have been described by many investigators.[47] The clinical symptoms resulting consist of severe pain in various parts of the body, especially in the limbs and the back, paresthesia and regional hypesthesia and anesthesia. These scattered sensory findings may assume a radicular or peripheral distribution. In the cases described

45. Kolisko, cited by Schlesinger, H.: Beiträge zur Klinik der Rückenmarks- und Wirbeltumoren, Jena, Gustav Fischer, 1898, p. 81. Taniguchi, K.: Deutsche Ztschr. f. Nervenh. **27**:148, 1904. Buchholz.[44c]

46. Lubarsch, O.: Ztschr. f. klin. Med. **31**:389, 1897.

47. (*a*) Francotte, K.: Rev. de méd., Paris **6**:394, 1886. (*b*) Nonne, M.: Deutsche Ztschr. f. Nervenh. **21**:396, 1902. (*c*) Lilienfeld, H., and Benda, C.: Klin. Wchnschr. **88**:729, 1901. (*d*) Miura.[44b] (*e*) Scanzoni.[44d]

by Maass [25] and Knierim [24] there was actual invasion of the rootlets and nerves by tumor cells. In the other cases, in spite of the symptoms referable to the nerves, no tumor involvement could be found on microscopic examination. Miura [44b] expressed the belief that the neuritis was caused by a poison given off by the primary neoplasm. He found degeneration of both the axons and the myelin. Auché,[48] in 9 cases of metastatic tumor with symptoms of peripheral neuritis, also observed degeneration and fragmentation of the myelin and swelling of the axons without any signs of tumor invasion of the nerves. He suggested that the neuritis was due to nutritional deficiency secondary to the cachexia produced by the cancer. Severe pain in the extremities described as neuritis was present in 7 cases of the present series. Unfortunately, none of the nerves was available for histologic study, so that it is not possible to describe the microscopic changes that occurred.

Aside from these specific findings in cancer metastatic to the nervous system, one must not overlook the fact that many nonspecific symptoms also occur. These consist of severe anorexia and loss of weight, generalized weakness, malaise and marked restlessness and irritability. The patients usually follow a fairly rapid downhill course to death.

Summary.—Tumors metastatic to the nervous system do not offer any specific symptom complex but may produce symptoms of a widely disseminated nature. For this reason the metastases are often overlooked unless one is aware of the presence of the primary tumor. Ferguson and Rees [49] expressed the belief that metastatic involvement of the brain should be suspected in every elderly patient in whom there is an acute onset of symptoms referable to the brain and in whom the wasting is out of proportion to the extent and duration of the neurologic symptoms. According to Elkington,[16] the clinical picture in a middle-aged person is characterized by a sudden onset of intense intracranial headache and severe wasting.

It seems, from the studies reported here, that there is no particular complex of symptoms that is diagnostic of metastatic involvement. I believe that any patient who presents symptoms of an intracranial involvement rather suddenly in middle life should have a careful investigation for a primary cancer elsewhere in the body. I agree, moreover, with Globus and Selinsky [50] that the following features should make one suspect that an intracranial metastasis is present:

1. Acute onset of symptoms referable to the brain, often of a focal or of a disseminated nature, in a middle-aged patient.
2. Presence of meningeal signs or of radicular pain.

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48. Auché, M.: Rev. de méd., Paris **10**:785, 1890.
49. Ferguson, F. R., and Rees, W. E.: Lancet **10**:738, 1930.
50. Globus, J. H., and Selinsky, H.: Arch. Neurol. & Psychiat. **17**:481, 1927.

3. Infrequency of signs of increased intracranial pressure with the exception of severe headaches, nausea and vertigo.
4. Infrequency of papilledema.
5. Extreme wasting with a rapid decline.

Before concluding this discussion, one should consider briefly certain recorded cases in which there was a discrepancy between the symptoms referable to the brain and the actual pathologic involvement by the metastatic tumors. Oppenheim,[51] Nonne,[47b] Siefert,[31] Spiller and Weisenburg [52] and Elzholz [44a] have all reported cases in which no metastases were found in the brain in spite of marked clinical symptoms of intracranial lesions. Oppenheim's patient with carcinoma of the stomach showed pupillary involvement, tonic convulsions and hemiplegia but had no gross cerebral lesions. In Nonne's cases of cancer of the gallbladder, cecum and pancreas, hemiplegia, aphasia and jacksonian epilepsy developed, but no gross or even histologic lesions of the brain were found. These investigators have suggested that carcinoma liberates a toxin that injures the brain. Elzholz quoted Müller and Klemperer, who studied the metabolism in cases of carcinoma and showed an increase in the nitrogen eliminated (the result of tissue destruction), a fatty change of the organs and a decrease of the alkaline content of the blood. On the basis of these findings he concluded that carcinoma can produce toxic changes. Saenger [44e] objected to this theory. He believed that if a careful examination is made of the brain, metastases will be found. He cited the case of a 46 year old woman with a primary cancer of the breast and cerebral symptoms. Gross examination of the brain revealed no lesions, but careful microscopic studies showed very tiny metastases to account for the symptoms. Saenger suggested that in cancer the cerebral symptoms resemble those seen with embolic processes and probably are of a similar nature. As will be seen from the pathologic studies reported here, the observations and suggestions of Saenger are probably correct, and if painstaking search is made in cases with clinical cerebral findings, tiny tumor emboli are usually found.

GROSS PATHOLOGY

Locations of Metastases.—Metastases to the central nervous system may involve any part of the brain, the cord or their coverings. By far the most common location of the involvement is within the brain. Table 6 shows the distribution of these lesions in the patients in the present series. There is a great diversity of opinion concerning the tendency of

51. Oppenheim, H.: Charité-Ann. **13**:335, 1888.

52. Spiller, W. G., and Weisenburg, T. H.: J. Nerv. & Ment. Dis. **33**:500, 1906.

the metastases to localize within certain regions of the brain. Krasting [1] and Kikuth [53] contend that the left hemisphere was more frequently involved than the right. This is not generally accepted and may be due to the fact that left-sided lesions more commonly produce obvious symptoms (such as aphasia) and hence lead to a more careful examination of the head. The localizations of the metastases in the brain in the present series are listed in tables 5 and 8. Of the total number of such metastases, 9 occurred on the right side, 18 on the left and 25 were bilateral. The difference in side of localization was not sufficient to be of any great significance. From the table on specific localization it appears that the metastases are usually scattered diffusely throughout the brain and show little tendency to localize within any particular region. Dickson [43] expressed the belief that most lesions occur in the frontal and temporosphenoidal regions and the cerebellum. The latter structure was involved in 27 of the present cases, and in 17 it was the only region involved. Similar high percentages of cerebellar metastases have been reported by Hare and Schwarz [20] and Willis.[4]

Probably one of the most widely accepted ideas concerning the localization of metastases within the brain is the one that the early or young lesions have a tendency to occur chiefly in the cortical gray matter or immediately below it at the border of the gray and white substance.[54] Courville,[7] in his study of melanoma, observed that the smaller nodules were frequently grouped about the sylvian fissure and were lodged in the cortex, subcortex and basal ganglions, in those regions supplied by the middle cerebral artery. Weller [38d] also, in his study on melanoma, described numerous cortical and subcortical nodules. Fischer [54b] explained this peripheral distribution on the assumption that cerebral metastases are blood borne, and since the center of the brain is supplied by twigs off the main vessels, while the periphery is supplied by direct continuations of the main branches, the tumor emboli naturally follow the main flow and lodge in the periphery. In spite of this accumulation of evidence regarding the frequency of peripheral metastases, many cases have been reported in which the metastases in the brain were found only deep within the white substance.[55] Whether these metastases were the only ones to lodge within the brain or whether they were the only ones to survive and grow while the cortical emboli remained

53. Kikuth, W.: Virchows Arch. f. path. Anat. **255**:107, 1925.

54. (*a*) Müller, F.: Ztschr. f. klin. Med. **16**:496, 1889. (*b*) Fischer, O.: Jahrb. f. Psychiat. u. Neurol. **25**:125, 1905. (*c*) Barnes, S.: Brain **28**:30, 1905. (*d*) Gallavardin.[35] (*e*) Fried.[36] (*f*) Weller.[38d] (*g*) Elkington.[16]

55. (*a*) Heinemann, J.: Virchows Arch. f. path. Anat. **205**:418, 1911. (*b*) Lewis, N. D. C.: Am. J. Psychiat. **5**:171, 1925. (*c*) Ogle, J. W.: Tr. Path. Soc. London **7**:5, 1856. (*e*) Fried.[36] (*f*) Globus and Selinsky.[50]

sterile is speculative. In my own studies I could find no direct evidence that metastases favored the cortical or subcortical regions. True enough, in many of the cases in my series the brain contained only cortical and subcortical nodules; however, this localization was not consistent, and there were many other cases in which the only metastases discoverable in the brain were deep within the white substance. In view of these findings it appears that in metastasis to the brain the tumor emboli become disseminated widely throughout this organ and begin to grow within both the cortex and the white substance. Just why tumor cells take hold in the cortex in one case and in the white matter in another case is unknown.

Number of Metastases.—The metastatic growth may assume many forms, appearing either as a single nodule of variable size and consistency or as extensive carcinomatosis. Most metastases, being blood borne, tend to be multiple rather than single. In the present series, 67, or

TABLE 8.—*Localization of Brain Metastases as to Side*

	Cases
1. Right cerebral hemisphere	4
2. Left cerebral hemisphere	13
3. Both hemispheres	15
4. Cerebellum only	14
5. Cerebellum and cerebrum (4 left; 2 right; 6 both)	12
6. Cerebrum and pons (3 right; 2 both)	5
7. Cerebrum, cerebellum and pons (1 left; 2 both)	3
8. Basal nuclei only	1

62 per cent, of the cases were characterized by multiple lesions. The predominance of multiple metastases has been observed by numerous investigators. Hare and Schwarz [20] found multiple lesions in 20 of 34 cases; Grant,[3] in 10 of 20 cases; Willis,[4] in 8 of 14 cases; Elkington,[16] in 9 of 17 cases; Davison and Horwitz,[12] in 3 of 7 cases. The number of these multiple lesions is most variable and depends a great deal on the time spent in search. The more careful and minute the gross examination, the more numerous will be the metastases discovered at autopsy. Fischer,[54b] in carefully examining the brain of a man who died of carcinoma of the lung, found over 90 metastases when the brain was cut at 1 cm. He stated that many more were present which were too small to be seen grossly.

Size of Lesions.—Before proceeding with a gross description of the various types of metastases, one might mention briefly the great variation in the size of these lesions. They may vary from pinpoint-sized nodules to huge masses that replace and destroy large portions of brain tissue. The latter are most frequent in cases in which the metastases involve silent areas of the brain and therefore have a chance to grow before the

patient dies. The more numerous the metastases, the smaller they appear at autopsy. This, no doubt, is due to the fact that the many small ones produce a lethal outcome in such a short time that the nodules do not have time to grow. In table 9 is shown the variation in size of some of the metastatic growths seen in the present series. The variation in size appears to be the same regardless of the primary source.

Structure of Metastases in the Brain.—In gross appearance the metastatic lesions are most variable, and unless one is acquainted with the numerous variations one might mistake some metastases for lesions of another category. For convenience the gross lesions can be divided into six different types, always keeping in mind that there is a great deal of overlapping among them.

(*a*) Soft Necrotic Type. In the present series this was by far the most common metastatic lesion. Early it appears as a small, circumscribed grayish white area that is somewhat softer than the surrounding

TABLE 9.—*Size of Metastases*

Site of Primary Neoplasm	Diameter of Intracranial Metastases	
	Smallest	Largest
Gastrointestinal tract	15.0 mm.	6.0 cm.
Adrenal	10.0 mm.	5.0 cm.
Skin (melanoma)	2.0 mm.	6.0 cm.
Kidney	4.0 mm.	5.0 cm.
Breast	5.0 mm.	8.0 cm.
Lung	2.0 mm.	7.5 cm.

brain tissue. It may be flecked with yellow areas or may contain tiny hemorrhages which give it a grayish brown appearance. At this stage, certain portions of the tumor may still appear firm while others are more friable and may have already broken down to form tiny cysts. As the lesion enlarges, it becomes softer, more necrotic and hence more sharply demarcated from the surrounding brain tissue. If it tends to merge with the surrounding brain, it may very easily be mistaken at this stage for an area of encephalomalacia. The softening and necrosis usually begin and are most marked in the center, producing a rounded, well defined lesion with definite central necrosis. Eventually lesions of this type become very soft and even semifluid. The necrotic material turns green, and often the semifluid substance falls away to leave scattered cysts throughout the metastatic mass. Ultimately, if such a metastasis continues to expand over a long period, the entire center is transformed into a greenish necrotic substance surrounded by a shaggy thick irregular wall, and then it bears a close resemblance to a brain abscess. One should remember that very few of the metastases actually continue to spread and reach this final stage, since most of the patients die before

this stage is reached. The nature of the primary neoplasm seems to have no bearing on the type of gross metastasis except for melanoma. The latter will be discussed separately in a later paragraph.

(*b*) Gelatinous Type (fig. 1 *A*). This type of lesion is fairly common but frequently, because of its unusual appearance, is not diagnosed until the histologic sections are obtained. It is often mistaken for some type of parasitic invasion of the central nervous system. Lesions of this type are of variable size but usually remain fairly small. Occasionally a large one is found which replaces a great part of the cerebellum (fig. 1 *A*). They appear as sharply demarcated, often multilocular cysts filled with a straw-colored or greenish sticky gelatinous material. The walls of these cysts are, for the most part, smooth and regular. However, careful examination will almost invariably reveal some areas of granular proliferating surface growth, which tends to invade the cyst, leaving a shaggy, irregular region. Often this granular material proliferates throughout the entire wall of the cystic lesion, gradually replacing the bulk of the lesion and leaving only a small gelatinous area in the center. As in all types of metastases, hemorrhage may result, transforming the gelatinous center into a green-purple discoloration.

(*c*) Granular Type. This type probably is a variation of the gelatinous cystic type of metastasis, since it is often observed associated with the latter. It is almost invariably small and appears as a firm, friable grayish mass which on cut section is extremely well defined and sharply demarcated from the surrounding brain tissue. It is usually a little softer than the uninvolved brain and often spongy in appearance. It fragments readily on section. Often it can be shelled out from the surrounding brain, leaving a smooth-walled cavity formed by the compressed brain tissue. In some areas of the cavity wall fragments of the tumor remain adherent, indicating invasiveness. As stated previously, the center of the granular mass may contain some greenish gelatinous material, but necrosis and softening apparently do not occur. Flecks of brownish discoloration may result from the tiny hemorrhages that are so commonly present within metastatic lesions.

(*d*) Hemorrhagic Type. Because of the hematogenous tumor spread with the subsequent vascular involvement, hemorrhages associated with encephalic metastases are extremely common and have been claimed by many to be one of the most characteristic gross features of such metastases. Aside from the hemorrhages associated with the other types of gross lesions, a primary hemorrhagic type occurs. When small, this appears as a soft reddish nodule or as a well circumscribed dark red mottled area surrounded by discolored brain tissue. Usually it is soft and granular but may be somewhat firmer and fleshy in consistency. The

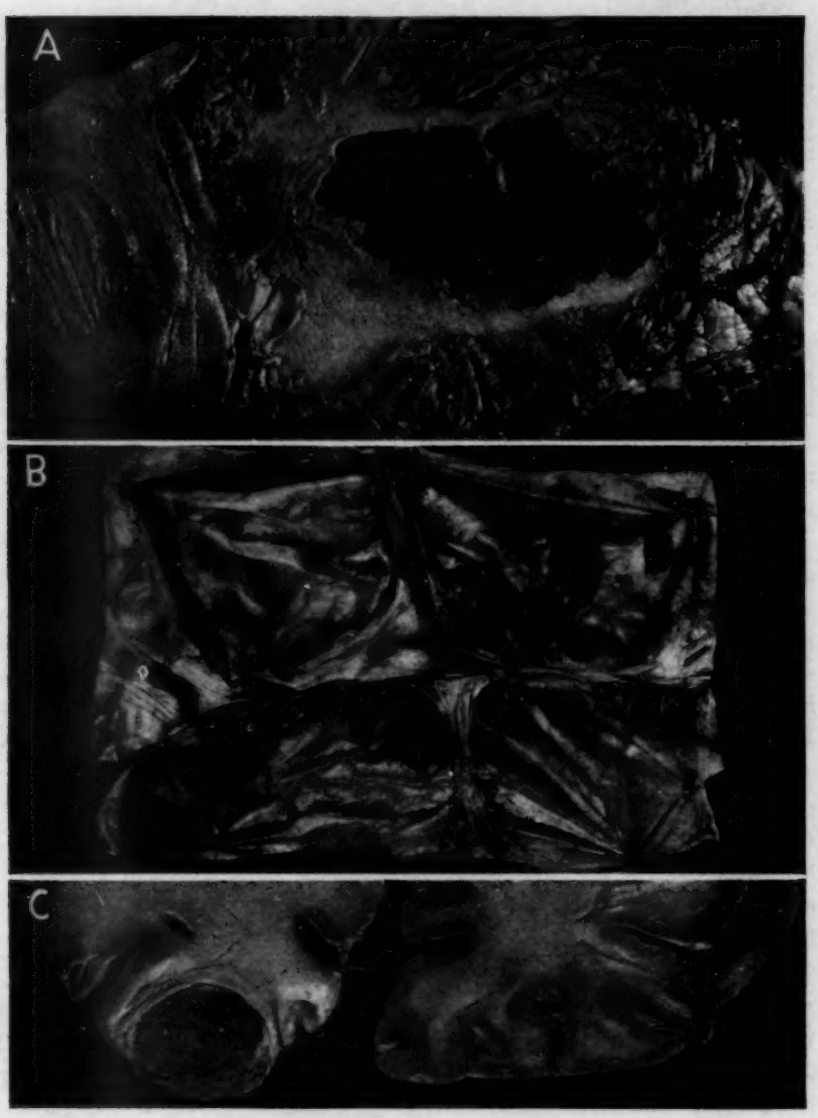

Fig. 1.—*A*, gelatinous metastasis from a primary tumor of the breast. The entire lesion is composed of a semifluid amorphous material. There is a thin granular layer around the outside of the metastasis. *B*, hard, firm metastases from a primary tumor of the breast. *C*, well outlined subcortical tumor (from same primary site as *B*) which appears to compress the surrounding brain tissue.

smaller, softer ones are often mistaken on gross inspection for tiny areas of hemorrhage. When the hemorrhagic tumors are large, they appear as well circumscribed large black spongy masses, which often replace large portions of a hemisphere and are usually situated deep within the white substance of the brain. Cut sections through them reveal in each instance a dark spongy mass, parts of which are firm and resistant and parts of which are soft, necrotic and hemorrhagic. The outer portion is the most firm. These tumors compress, but do not seem to invade the surrounding brain tissue and often can be shelled out, leaving a very smooth-walled cavity. The surrounding brain tissue is frequently discolored and is occasionally filled with small hemorrhages. The large hemorrhagic metastasis resembles angioma and is often mistaken for such a lesion.

Because of the vascular injury and rupture, actual hemorrhage sometimes occurs, destroying the involved brain tissue. Tumor cells then grow and proliferate within these hemorrhagic, necrotic regions. Such lesions are not true hemorrhagic metastases, but are better classified as actual hemorrhages into the brain tissue with secondary tumor growth. If the patient lives sufficiently long, the neoplastic cells may proliferate enough to replace most of the original hemorrhagic area and thus produce an actual hemorrhagic metastasis. The hemorrhagic metastasis can, therefore, arise in two ways: first, through an actual growth with secondary bleeding within the lesion and, second, through a primary hemorrhage into brain tissue with secondary tumor growth within the hemorrhagic area. Probably the former process is the most frequent in view of the structure of these tiny lesions and their sharp demarcation from the adjacent brain tissue.

(*e*) Hard Type (fig. 1 *C*). These are always small and extremely well circumscribed. They are firm and hence are sharply demarcated from the surrounding brain tissue (fig. 1 *C*). They are usually whitish or gray in color and often rubbery or even gritty in consistency. They have a tendency to be more frequent in the cortex or subcortical regions of the brain, often projecting from the cortex into the subarachnoid space. In spite of their demarcation from the adjacent brain, they usually cannot be shelled out but seem to be adherent to the surrounding tissue. Even these lesions are occasionally flecked with tiny brownish specks representing petechiae within the tumor. Of the different types of metastases this is the most readily recognized. In the present series, lesions of this type had their primary origin either in the breast or in the gastrointestinal tract.

(*f*) Melanotic Type. Because of the added feature of pigmentation, these metastases must be considered in a separate category. They are almost always multiple and small, resembling to a large degree those

lesions described as the hard type, except that they are pigmented. They vary in diameter from a few millimeters to a few centimeters. Although appearing well circumscribed, they are invasive and become firmly embedded within the brain tissue. Melanotic metastases are not always pigmented, the nonpigmented ones appearing gray and being identical with the "hard type" except that they are a little softer and much more invasive. As a rule, one has little trouble in identifying this type of lesion.

Structure of Metastases in the Leptomeninges.—Leptomeningeal metastases have been reported in the literature under the name of "carcinomatosis of the meninges" and were first described by Saenger.[44e] The first accurate pathologic description was published by Lilienfeld and Benda,[47c] in 1901. Since that time many reports have appeared.[56]

Grossly, the meninges even on careful scrutiny may appear normal. The carcinomatous involvement may be invisible to the naked eye and appear only on microscopic study. Usually, however, careful examination will reveal even the early lesions. These appear as milky discolorations or as granular or fibrous alterations of the membranes. The leptomeningeal thickening may become marked, often reaching a few millimeters in thickness, especially over the base of the brain, where the basilar structures become completely obliterated. On cut section this type of meningeal involvement is quite obvious and easily detected.

The leptomeningeal metastases may assume a nodular form. These nodules often appear as fine tubercle-like elevations, which are barely visible to the naked eye and are scattered diffusely throughout the meninges, especially along the sulci in the course of the vessels. At times they are less numerous but larger and appear as firm irregular masses that protrude from the meninges and produce small depressions in the underlying brain tissue. Occasionally there occurs only a single large flat tumor mass that involves a large area of the leptomeninges. This is firm, granular and grayish brown. It may be so flat that it causes little or no compression of the underlying brain, or it may be globoid, forming a huge defect. When it occurs along the base, there may result extensive involvement of cranial nerves as well as invasion and destruction of the pituitary gland.

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56. Bertrand, I., and Aronson, L.: Rev. neurol. **37**:145, 1921. Siefert, E.: Arch. f. Psychiat. **36**:720, 1903. Rindfleisch, W.: Deutsche Ztschr. f. Nervenh. **26**:135, 1904. Scholz, W.: Wien. klin. Wchnschr. **47**:1231, 1905. Schwarz, E. and Bertels, A.: Deutsche Ztschr. f. Nervenh. **42**:85, 1911. Stursberg, H.: ibid **33**:68, 1907. Sicard, J. A., and Gy, A.: Rev. neurol. **23**:1092, 1908. Marchand: München. med. Wchnschr. **54**:637, 1907. Lissauer, H.: Deutsche med. Wchnschr. **16**:561, 1911. Pachantoni, D.: Arch. f. Psychiat. **49**:396, 1912. Heinemann.[55a] Nonne.[47b] Rehn.[23] Hassin.[29]

When the involvement of the meninges is melanotic, the lesions differ only in that there might be associated discoloration due to the pigment. With the early diffuse type, the meninges may appear uninvolved except for slight discoloration. If the melanotic lesions are nonpigmented, their exact nature usually remains undetermined until the microscopic sections are obtained.

Structure of Dural Metastases (fig. 1 *B*).—Metastatic lesions involving only the dura have been described by numerous investigators.[57] They are fairly common, occurring in 20 of the present cases. At times the dura merely appears thickened in the involved areas. In these regions the pachymeninx is grayish white, friable and often firmly adherent to the cranium. When large areas of the dura are thus diffusely invaded by the tumor tissue, the changes are easily discerned on careful examination, although they may be overlooked on cursory study.

Occasionally the tumor infiltration produces a rupture of the intradural vessels, resulting in a dural hemorrhage. In such cases a fine layer of blood intermixed with tumor cells and dural tissue is layered over the inner surface of the dura and is covered by a thin membrane which is composed of a dissected portion of the original dura (Baker [58]).

The nodular dural lesions are more common than the diffuse. They may vary from small white lesions, a few millimeters in diameter, to huge globoid masses, which may be very firm or may appear hemorrhagic and soft. They are often infiltrative and penetrate through the dura to erode into the overlying skull. These large fungoid masses usually project from the inner surface of the dura, to which they are attached by a wide base. They may also extend through the dura to form a thin sheath of neoplastic tissue on its outer surface. Occasionally erosion of the skull results so that the dura is firmly attached to the overlying bone. These huge tumors are firm and smooth surfaced. On section they appear spongy or granular and usually contain areas of gross hemorrhage or necrosis. They closely resemble in gross appearance meningioma, and like that tumor extend inward to obliterate the underlying subarachnoid space and produce huge indentations in the underlying tissue. Melanotic lesions are usually small and differ only in their color, which is blue-black because of the pigmentation.

MICROSCOPIC PATHOLOGY

In order to follow in some detail the histologic appearances of metastatic tumors, 92 cases were studied. Sections were prepared with the

57. Westenhoeffer, M.: Virchows Arch. f. path. Anat. **175**:364, 1904. Marinesco, G., and Goldstein, M.: Ann. d'anat. path. **12**:101, 1935. Dahman, F.: Ztschr. f. Krebsforsch. **3**:300, 1905. Fischer.[54b]

58. Baker, A. B.: Arch. Path. **26**:535, 1938.

following stains: hematoxylin-eosin, azocarmine, Holzer, Bodian, Perdrau, thionin for Nissl substance and Mayer's mucicarmine. Since the beginning lesions are usually obliterated in the larger tumor masses, many of the smaller lesions were sectioned serially in an attempt to observe some of the early alterations prior to their obliteration by tumor and cellular overgrowth. The individual cases in the series will not be discussed, but a composite description will be attempted from a microscopic study of the individual neoplasms.

Early Formation of Tumor Metastases.—Most metastases appear to be hematogenous. Tumor cells can be found within some of the tiny arteries of the metastases or within the vessels of the still uninvolved brain (fig. 2*A*). These cells may completely occlude the lumen or may stimulate extensive endothelial proliferation, which together with the tumor cells results in vascular occlusion. The occlusion produces ischemia and softening of the surrounding brain tissue as well as injury and weakening of the involved vessel. The intravascular tumor cells then proliferate and grow irregularly through the injured vascular wall into the fragmented brain tissue, which now offers an excellent medium for their growth. At this stage the neoplastic cells partially or even completely obliterate the involved vessel and form a small tumor nodule situated within an area of softened brain tissue. Often the remnants of the involved vessel can still be made out within the neoplastic cells.

In cases of melanoma, very early metastases can be studied easily because of the pigmentation of the cells. Numerous scattered vessels become filled with pigmented neoplastic elements. These do not necessarily occlude the lumens but may be intermixed with erythrocytes in an artery whose lumen remains patent. The long spindle-shaped pigmented cells soon migrate through the vessel wall to reach the perivascular space, where they proliferate. Some tumor cells can actually be observed lying within the wall of the vessel.

If the neoplastic cells become implanted and begin to proliferate within the brain, they may assume numerous appearances, depending on their mode of spread and their nature. It is these different appearances or tumor types that one is most accustomed to seeing in a routine study of older metastases. For convenience, the metastases have been divided into seven different histologic types, namely: epithelial, perivascular, encephalomalacic, gliotic, vascular, hemorrhagic and melanotic.

Histologic Types of Metastases in the Brain.—(*a*) Predominantly Epithelial. By far the most common type of metastasis in the brain is that which is predominantly epithelial. It is represented by two distinct varieties of lesions. The first results from proliferation of the tumor cells from a single focus to form a large solid mass. Numerous blood

vessels are present, and from these vessels long strands of connective tissue extend outward to encircle groups of the neoplastic cells. As the tumor enlarges, its center becomes necrotic and hemorrhagic (fig. 2*B*). This central necrosis may spread very rapidly, replacing almost all of the tumor elements. It loses all structural characteristics and eventually assumes a homogeneous or even hyalinized appearance. Surrounding this central necrosis is a zone of shrunken tumor cells, and outside of these is a layer of fairly well preserved cells. In some cases secondary infection occurs within the destroyed central elements. The involved vessels become filled with polymorphonuclear leukocytes, which soon migrate into the necrotic tumor tissue to fill the entire area with pus cells, producing the appearance of an abscess. Surrounding such a central abscess are scattered clumps of neoplastic cells intermixed with softened fragmented brain tissue. Usually numerous erythrocytes are intermixed with the pus cells owing to the degeneration and rupture of the involved blood vessels.

The second variety of epithelial lesion is produced by the spread of the tumor cells from the original focus to the perivascular spaces of the neighboring vessels, where they then proliferate from numerous adjacent foci. The proliferating elements around the various vessels fuse to form a large nodule. In this tumor the neoplastic cells assume a definite lobular arrangement, owing to their perivascular growth, even though the tumor elements have fused to form a large continuous tumor mass (fig. 2*C*). Degeneration within the tumor occurs only when the central vessels show extensive endothelial proliferation with partial or complete vascular occlusion. The degenerative process, therefore, is lobular rather than central and involves any lobule regardless of its position, be it central or peripheral. The degenerative process follows a definite pattern. The cells in the center of the lobule become swollen, their cytoplasm appears clumped, and the nuclei shrink and stain very deeply. The now coarsely granular cytoplasm of the involved cells fuses to form a single central mass, and their small pyknotic nuclei often entirely disappear (fig. 2*C*). The cells adjacent to this central degeneration soon show similar swelling and granular alteration. They eventually merge with the central area of degeneration, which thus gradually increases in size until it involves most of the lobule, only a thin rim of intact neoplastic cells remaining. In a single tumor all stages in this process of granular degeneration can be observed in the different lobules. Occasionally a few adjacent lobules which have undergone complete destruction will fuse to form a huge mass of granular degeneration that replaces a large part of the entire neoplasm. This granular debris may be further altered, the coarse granules becoming very fine or even losing all their structural characteristics to appear homogeneous.

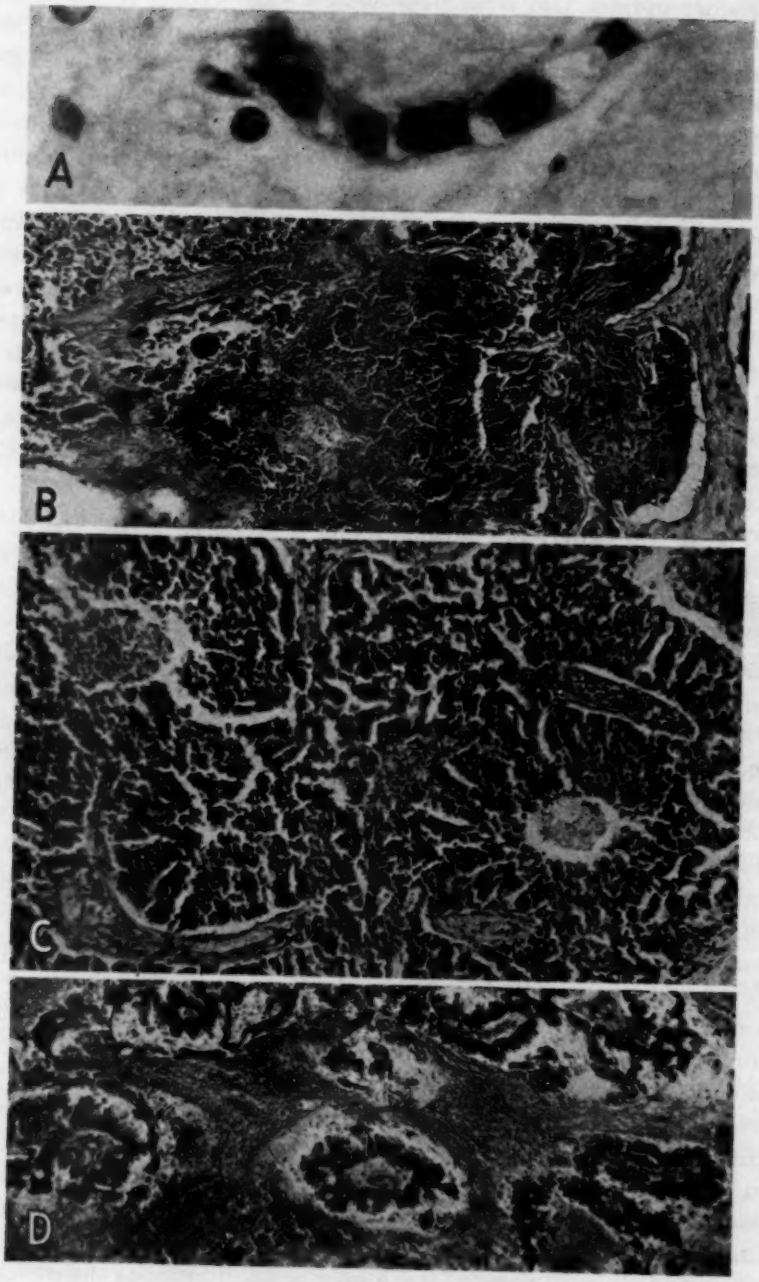

Figure 2

(See legend on opposite page)

In some of the glandular metastases, especially those from mammary, intestinal or pancreatic tumors, the cells apparently retain their capacity for secreting mucin, and the degenerative process, although similar to that just described, is a little different in some of its histologic details. The cells in the centers of the lobules at first appear somewhat foamy and vacuolated. The vacuoles gradually increase in size and eventually fill the entire cell body, which now appears swollen and rounded. The cell nuclei become shrunken, pyknotic and eccentrically placed. These swollen cells eventually rupture, extruding their nuclei and producing a large vacuolated area filled with the amorphous remnants of the destroyed cells. More and more of the surrounding tumor cells undergo similar vacuolation and rupture into the central area of degeneration, which continues to enlarge until it replaces the entire lobule. In some regions the degenerated lobules fuse to form a huge mass of amorphous stringy material that replaces large areas of the tumor. Only an irregular rim of partially altered neoplastic cells remains around the periphery of the degenerated elements. These tumors appear grossly as gelatinous-like structures and have been listed with the gross gelatinous tumor types.

(*b*) Predominantly Perivascular. This type of metastatic nodule is somewhat smaller than the epithelial. It is composed of scattered islands of perivascular tumor cells separated by apparently normal or somewhat altered brain tissue(fig. 2 *D*). The tumor cells in some regions merely fill the perivascular spaces while those in other areas proliferate outward to invade the surrounding brain tissue. The proliferation of neoplastic cells usually occurs in an outward direction, so that the vessel itself is not involved, and its lumen remains patent for a long time in spite of the tumor activity about it. Occasionally intimal changes do occur, the

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EXPLANATION OF FIGURE 2

A, large tumor cells within a cerebral vessel. The faint outline of the capillary wall can be made out. These cells, which are metastatic from a primary tumor of the skin (melanoma), are pigmented and therefore are easily detected and differentiated from the blood cells. Hematoxylin-eosin stain.

B, epithelial type of metastasis showing extensive central necrosis. There is still some intact tumor tissue around the periphery of the lesion. The site of the primary tumor was undetermined. Hematoxylin-eosin stain.

C, epithelial metastasis of the lobular type. The neoplastic elements are arranged around the blood vessels, forming large lobules which lie adjacent to or fuse with one another. The primary site of the neoplasm was the gum. Hematoxylin-eosin stain.

D, perivascular metastasis from a primary tumor of the lung. The tumor cells are all arranged around the cerebral blood vessels with apparently normal brain tissue between the neoplastic elements. Hematoxylin-eosin stain.

endothelium proliferating to occlude the vessel partially or completely. If occlusion is partial, the perivascular tumor cells remain intact, but the adjacent brain tissue undergoes degeneration and becomes softened and filled with fat granule cells. In such cases the softened brain tissue will eventually be replaced by dense bands of glial fibers which stretch from one tumor lobule to the next. If the vascular lumen is completely occluded by the endothelial overgrowth, the tumor cells as well as the adjacent brain tissue undergo degeneration. The involved tumor cells eventually disappear, leaving only a group of occluded vessels surrounded by necrotic tissue, the tissue closest to the vessels containing a few remnants of the neoplastic elements.

(*c*) Encephalomalacic. This unusual type of lesion consists almost entirely of softened fragments of brain tissue. The involved tissues have lost much of their tinctorial properties. The cellular elements within such a lesion vary with the age of the process. The earlier lesions are filled with fat granule cells, while the older ones show some glial increase. The involved vessels are distended and occasionally surrounded by mononuclear cells. A few of the smaller vessels rupture, producing tiny hemorrhages. Scattered clumps of neoplastic cells can be found throughout the softened brain tissues, and it is these tumor elements that differentiate this lesion from a typical infarction. Often these neoplastic cells are very scarce, and but few groups are observed even after a most careful search.

It is obvious that such an area of softening can be caused only by occlusion of a moderate-sized artery by a tumor embolus. Frequently the exact vessel with its tumor cells is difficult to find, and serial section of the tissues surrounding the actual lesion is necessary to reveal the source of the involvement. The presence of tumor cells within the area of softening indicates that some of the neoplastic elements have broken off from the area of thrombus and have reached the infarcted tissues through the smaller vessels.

(*d*) Gliotic. In some metastases in the brain the tumor cells, after their implantation, seem to stimulate a most extensive glial overgrowth (fig. 3 *A*). This proliferation of the glial elements continues until a large tumor nodule is formed that closely resembles a primary tumor of the brain. There is usually a great multiformity in the shape and size of the glial cells, so that there is close simulation of glioblastoma multiforme. The majority of the cells consists of bipolar and unipolar spongioblasts, but astrocytes, giant astrocytes and astroblasts may also be present. Giant cells are extremely frequent, and the astroblasts often proliferate to form numerous pseudorosettes. The blood vessels within these tumors are numerous and show the characteristic changes described in glioma.

Their endothelial proliferation is extensive, and the adventitial overgrowth is often so marked that many collagenous fibers spread outward into the surrounding glial elements. Hemorrhage and necrosis are present. There is no sharp demarcation between these tumors and the surrounding brain tissue. The glial elements gradually merge into the adjacent brain tissue with a decreasing amount of cellular activity (fig. 3*A*). Some astrocytic increase and proliferation can be seen for considerable distances from the active process.

Although tumors of this type closely resemble and may be confused with primary glioma, certain peculiarities aside from the presence of metastatic cells are present that suggest their metastatic nature. Usually they contain much more connective tissue than does glioma. This is especially noticeable with the azocarmine and Perdrau stains. The collagenous fibers ramify from the vascular adventitia into the tumor. In some areas the collagenous fibers are so numerous that they actually replace some of the glial elements. Often no vessels can be found near these collagenous elements, and their actual origin remains unsolved. The presence, therefore, of large amounts of collagen should make one suspect a metastatic lesion. In such cases a careful search should be made throughout the tumor for some remnants of the original tumor cells. Such epithelial elements are usually distorted and partially destroyed by the glial reaction and therefore may be difficult to recognize. Their presence, however, establishes beyond a doubt the true nature of the tumor growth.

(*e*) Vascular. This is a very unusual form of metastasis, occurring in but 1 case of the series. The metastatic nodule is composed almost exclusively of large, fairly regular blood channels with only a few tumor cells scattered between the vessels (fig. 3*B*). These vessels are composed of a layer of flattened endothelial cells and a layer of connective tissue. They may or may not be filled with erythrocytes. Occasionally the large distended vascular structures are situated very close to one another, thus resembling cavernous angioma. Often only a single layer of tumor cells surround them; at times the neoplastic elements proliferate outward to merge with those from an adjacent vessel. Fine connective tissue strands extend from the vessels to ramify between the areas of tumor. Vascular occlusion and necrosis usually do not occur.

(*f*) Hemorrhagic. This type is characterized by extensive hemorrhages that comprise most of the tumor area. The erythrocytes obliterate all other elements and even tear into the adjacent brain tissue to produce scattered foci of hemorrhage and necrosis. Many of the red cells become lysed, distributing free pigment irregularly in the tumor mass. Usually the ruptured vessels cannot be found in the large hemor-

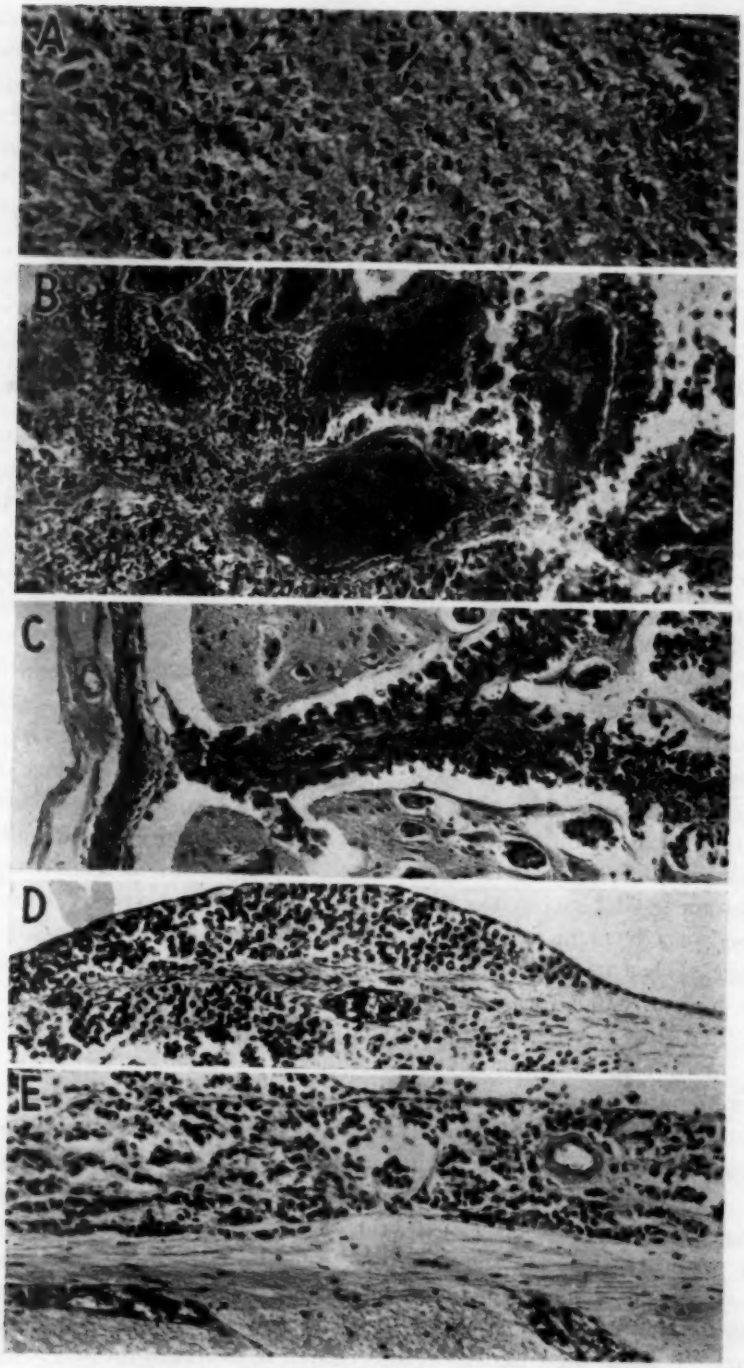

Figure 3

(See legend on opposite page)

rhagic nodule. Tiny islands of tumor cells are scattered throughout. These neoplastic elements are usually perivascular. The central vessel is often distended and occasionally ruptured, with red cells streaming out into the tumor elements. In those cases in which the central vessel is uninvolved, red cells frequently infiltrate from the periphery and merge with the neoplastic elements.

(*g*) Melanotic. The metastases of melanoma are placed in a separate group primarily because of their pigmentation. The tumor cells are either spindle shaped or large and oval with polymorphic nuclei. The presence of the melanin within them simplifies their identification and facilitates the study of their spread. This is chiefly hematogenous, and numerous widely scattered arteries can be found filled with typical melanoma cells. The cells begin to proliferate within these vessels, migrating through or replacing the vessel wall and producing a definite tumor nodule. From this focus the neoplastic elements apparently spread along the perivascular spaces to the adjacent vessels, which they surround and from which they extend outward into the adjacent tissues. Some of these small perivascular nodules may eventually fuse to form a larger lesion. As a rule, the melanotic metastases tend to remain as numerous, scattered, fairly small foci. Occasionally their growth is very rapid and many lobules fuse to form a huge solitary melanotic lesion. The melanoma cells are often separated into clusters by connective tissue bands, giving the tumor an alveolar arrangement. Melanin may or may not be present. When present it may form massive brown globules that obliterate much of the underlying cellular structure.

EXPLANATION OF FIGURE 3

A, extensive glial overgrowth produced by metastases from a primary tumor of the ovary. Note the resemblance to primary glioma of the brain. Hematoxylin-eosin stain.

B, vascular metastasis composed primarily of large blood channels. Tumor cells are present between the vascular structures. The site of the primary tumor was a kidney. Hematoxylin-eosin stain.

C, longitudinal section of a cerebral vessel showing tumor cells from a primary tumor of the lung as they extend along the perivascular space from the intracerebral lesion to the subarachnoid space. Hematoxylin-eosin stain.

D, extension of a metastasis from a primary tumor of the stomach into a ventricle. An intact layer of ependyma still covers the tumor cells. Hematoxylin-eosin stain.

E, complete replacement of the subarachnoid space by tumor cells metastatic from a primary tumor of the breast. Note the extension of the neoplastic elements along the perivascular spaces of the subarachnoid vessels into the underlying brain tissue. Hematoxylin-eosin stain.

Cellular Structure of Metastases as Compared with Primary Foci.—Little can be added from these studies concerning the detailed cellular structure of metastases within the brain. In most cases there was a remarkable resemblance between the primary lesion and those within the brain. A brief review of some of the cell types from the different primary sources might be worth while.

(*a*) Lung. Three distinct cellular types of metastasis occur, resembling the three varieties of primary carcinoma, namely: the squamous cell, the columnar cell of adenocarcinoma and the small round or undifferentiated cell (oat cell). The last type consists of solid masses of small dark cells that are full of mitoses and spread fairly rapidly by direct invasion of the adjacent brain tissue. The typical adenocarcinoma is composed of columnar or cuboidal cells arranged in solid trabeculae or even in papillomatous masses. Often many of the small, undifferentiated cells can be seen intermixed with the more glandular elements. Occasionally typical adenocarcinoma of the lungs will give rise to cerebral metastases that are composed almost entirely of the small, undifferentiated dark cells.

(*b*) Breast. Three different metastatic cell types arise from the breast. One is the typical squamous cell carcinoma. A second consists of small, round, deeply staining cells which are arranged in tiny clumps or around an empty space to give an acinous appearance. These cells are very uniform in appearance and usually arise from medullary or sometimes from adenomatous carcinoma of the breast. The most common metastatic type is typically glandular, composed of columnar or cuboidal cells. These cells may lose their glandular arrangement and appear as large clumps of discrete cells. They are characterized by their tendency to be foamy and vacuolated. In many, the entire cytoplasm is replaced by vacuoles, while the nucleus is displaced peripherally. Often they are separated by a loose stroma filled with mucin. These metastases arise primarily from gelatinous or medullary carcinoma of the breast.

(*c*) Gastrointestinal Tract. Only two types of tumor cell metastases were observed. The most frequent is very cellular and is composed of masses of fairly discrete, closely packed cells. Their nuclei are somewhat irregular and may be vesicular or deeply staining. The cell cytoplasm varies in amount and is often vacuolated and foamy in appearance. When the vacuoles fill the cell, the nucleus may be displaced peripherally, giving these cells a signet ring appearance. Giant cells and mitoses are frequent. Prominent bundles of connective tissue are present within these tumors and divide the cells into tiny clumps, producing an alveolar-like arrangement.

A less common type of lesion is the typical glandular metastasis, in which the cells are columnar or cuboidal and are arranged in trabeculae or appear as papillomatous tufts with loose connective tissue filling the cores of the tufts.

(*d*) Kidney. The appearance of the tumor cells in all our cases of metastasis from the kidney was uniform. They are large clear cells, somewhat irregular in outline but closely packed into tiny cords containing no lumens. The cell nuclei are oval and stain fairly deeply. Many of the cells are partially or completely filled by tiny vacuoles. Scattered throughout the tumor are isolated cords of somewhat darker staining cells. Fine strands of connective tissue ramify throughout, dividing the tumor cells into small clumps, producing an alveolar arrangement.

(*e*) Bladder. The metastases were typical squamous cell carcinoma.

(*f*) Uterus. The uterine tumors give rise to typical metastatic adenocarcinoma with the cellular part composed mostly of columnar epithelium. In some areas rapid proliferation occurs, forming large masses of small dark cells with tiny, deep-staining nuclei. There appears to be direct transformation of the columnar elements into the more rapidly growing small isolated undifferentiated cells.

(*g*) Testis. The cellular structure of metastases from testicular tumors is most variable. The cells are arranged in irregular clumps, surrounded by connective tissue and blood vessels. The cells are variable in shape, often being huge and multinucleated and containing either granular or vacuolated cytoplasm. The nuclei are most irregular in size and shape; they are usually large, dark and possessed of a nucleolus. Frequently large areas of the tumor are replaced by vacuolated cells. These vacuoles may replace the entire cell and may even rupture the cells to produce tiny cysts within the tumor.

(*h*) Sarcoma. Metastatic sarcomatous lesions of the central nervous system, exclusive of melanoma, are relatively uncommon, although they do occur (Junghanns [59]; Harding and Courville [60]; Braune [61]). Only one was observed in the present series. These metastases apparently do not present any unusual characteristics. They are usually multiple, firm, sharply demarcated from the surrounding brain tissue and frequently flecked with tiny brown specks of blood pigment. When the cerebral metastases arise from primary bone sarcoma, they are often extremely firm and gritty and contain irregular spicules of bone and osteoid tissue. Histologically, sarcomatous metastases within the brain also show a resemblance to the primary lesion. Those from bone

59. Junghanns, H.: Deutsche Ztschr. f. Chir. **224**:418, 1930.
60. Harding, W. G., and Courville, C. B.: Am. J. Cancer **21**:787, 1934.
61. Braune, B.: Arch. f. Kinderh. **112**:193, 1937.

sarcoma frequently contain large numbers of osteoblasts as well as immature spindle-shaped neoplastic elements.

Secondary Spread Within the Brain.—Most metastatic tumors of the brain even histologically appear to be sharply demarcated from the surrounding tissues. It is only by careful study, often with special stains, that one is able to detect the extensive involvement of the adjoining structures. In spite of the fact that these tumors seem only to compress the surrounding tissues, they are histologically definitely invasive and tend to spread within the brain either by direct extension from the main tumor mass or by invasion along the perivascular spaces of the adjoining vessels.

(*a*) By Direct Extension. In the gliotic type of metastases, this mode of spread is evident since the tumor gradually blends with the surrounding brain tissue. However, in the remaining forms this type of spread is not so obvious, although it does occur. These tumors may appear to be sharply circumscribed, but as they increase in size the proliferating cells compress the surrounding brain and the various tumor lobules extend outward to produce distinct indentations within the surrounding tissues (fig. 2 *B*). Usually there does not result actual softening of the involved brain tissues. When softening occurs, the neoplastic elements invade much more rapidly and irregularly, often losing their uniform lobular arrangement.

(*b*) By Perivascular Routes. This is the most frequent mode of extension for metastatic tumors. The neoplastic elements spread along the perivascular spaces into the tissues surrounding the main tumor mass. Many of the blood vessels within the adjacent brain tissue become surrounded by tumor cells, which may be deposited in a single layer or may be so numerous that they completely fill the perivascular spaces. Frequently the tumor cells continue to proliferate and extend outside the perivascular spaces to involve the surrounding brain tissue. When the perivascular cell spread is entirely outward, the vessel itself remains uninvolved and the surrounding brain tissue appears intact. In most cases, however, the perivascular tumor growth produces definite narrowing of the lumens, either by compression of the vascular walls or by secondary endothelial proliferation. This occlusion naturally results in rapid necrosis of the surrounding brain tissue, and since this softened tissue forms an excellent medium for the tumor's growth, there results a fairly rapid and often irregular spread of the tumor into the injured areas. Occasionally this perivascular spread is extreme, and vessels far removed from the main tumor mass become surrounded by layers of the neoplastic elements. This mode of dissemination is analogous to the well recognized metastasis by lymphatic channels in other parts of the body.

(*c*) By Pial and Ventricular Routes. Tumors near the cortex of the brain may spread by direct extension through the cortex to the pia. At this point the spread seems to stop, the pia appearing to act as a barrier preventing the neoplasm from rupturing into the subarachnoid space. When the tumor cells are extremely active and invasive, they do not stop at the margin of the pia but readily break into the subarachnoid space. More commonly, however, the subarachnoid space becomes involved by an extension of the neoplastic cells along perivascular channels (fig. 3 *C*). One can frequently follow this spread along the perivascular channels of the adjoining vessels.

When a metastasis occurs in the vicinity of a ventricle, the tumor cells spread from the main tumor mass to the surface of the ventricle. By continued growth, the tumor occasionally protrudes into the ventricle and may be covered by a stretched but still intact layer of ependyma (fig. 3 *D*.). Eventually the ependyma ruptures and portions of the neoplastic elements break off and become implanted throughout the ventricular system.

Alterations in Tissues Surrounding Metastases in the Brain.—Numerous changes occur within the tissues adjacent to metastatic lesions.

(*a*) Softening. Softening and fragmentation of the brain adjacent to a metastatic lesion is extremely common, although not constant. This destruction may surround the entire tumor or may occur in only parts of its circumference. The softened brain shows all stages of degeneration. Portions may show only tinctorial loss and beginning patchy or diffuse demyelination. Other areas may show complete destruction and invasion by scavenger cells. Extensive glial proliferation within these softened areas is never observed. Hemorrhages and vascular changes do occur.

(*b*) Vascular Changes. Vascular changes are one of the most constant findings in areas immediately adjacent to a metastatic lesion. They are observed regardless of whether the surrounding tissue is injured or intact. They consist chiefly of extensive endothelial proliferation, which may be so marked that it produces complete obliteration of the lumen with secondary softening of the surrounding brain elements. In an occasional case, the endothelial overgrowth is so extensive that it forms a definite layer between the tumor and the surrounding tissues. Other vascular changes consist of adventitial proliferation and occasionally vascular rupture with hemorrhage.

(*c*) Hemorrhages. Various-sized hemorrhages are common around metastatic tumors. In some instances only petechiae or diffuse extravasations occur while in others the bleedings may be very large and destructive. Curiously, the large hemorrhages usually are situated immediately along the border of the metastatic tumor, separating it from

the adjacent brain. They may form a complete band around the tumor mass or may be present only along a portion of its circumference. In the larger lesions the ruptured vessels are usually not discovered.

(*d*) Glial Reaction. The degree of glial reaction around the metastatic tumors is most variable but as a rule is not extensive. In most cases little gliosis is observed, even with special stains. Around some of the tumors there does occur a definite increase in glia, while in an occasional case there results most striking and extensive gliosis. Tumor cells are never seen outside the glial covering.

(*e*) Nerve Cell Changes. Alterations within the nerve cells of the brain have been reported by various investigators. Fischer [54b] reported in his cases mild chromatolysis of the nerve cells throughout the brain. Those adjacent to the tumor were most severely involved. Spiller and Weisenburg [52] recorded chromatolysis, swelling of the nerve cells and occasional eccentricity of the nuclei. In their cases, curiously enough, the alterations of the nerve cells were always diffuse in spite of the fact that the clinical symptoms were of a focal nature. Hassin and Singer [62] observed similar changes in the ganglion cells. In some areas they detected liquefied cells and neuronophagia. Most of these investigators have advocated some toxic effect of the carcinomatous tissues on the nerve cells of the brain.

In the cases of the present series alterations occurred in ganglion cells situated adjacent to the neoplastic lesion or within the softened brain tissue. Some cells were swollen, rounded, and their processes fragmented, while others were shrunken and pyknotic with small, eccentrically placed nuclei. In the latter, the Nissl substance was clumped or entirely absent, and the cell processes were often fragmented or narrowed and elongated. Sections obtained at greater distances from the tumor elements revealed no abnormalities of the nerve cells. In none of these cases was it possible to find the so-called toxic ganglion cell changes described in the literature.

(*f*) Other Changes. The brain tissue other than that directly surrounding the tumor masses was usually uninvolved. A few areas of focal demyelination or tinctorial alteration did occur, but these changes were invariably associated with vascular disease, usually of an arteriosclerotic nature. No changes were observed that were compatible with the effects of a toxin liberated by the neoplastic elements.

Metastatic Involvement of the Leptomeninges.—In some cases only a few tumor cells are scattered diffusely throughout the subarachnoid space. These cells may be discrete or clumped, or may assume a perivascular arrangement. When the involvement is mild, the pia is not thickened and the tumor cells do not penetrate along the vessels into the superficial layers of the cortex.

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62. Hassin, G. B., and Singer, H. D.: Arch. Neurol. & Psychiat. **8**:155, 1922.

In other cases the leptomeningeal invasion is more extensive and the tumor cells infiltrate into every area, replacing the arachnoid trabeculae and obliterating the blood vessels. Connective tissue fibrils ramify outward from the walls of the vessels to divide the neoplastic elements into tiny clusters or columns. Lymphocytes, plasma cells and fat granule cells are intermixed with the tumor cells. In the more extensive metastases, the pia does become thickened. This membrane acts as a barrier to the neoplastic elements, although invasion through it can occur; the tumor cells form tiny tumor nodules within the underlying brain tissue. Usually, however, the tumor cells do not penetrate through the thickened pia, but pass along the perivascular spaces of the subarachnoid vessels to reach the brain tissue (fig. 3 *E*). In most cases serial sections will reveal such involved vessels extending into the deep layers of the cortex.

The actual structure of the neoplastic elements varies from case to case. In some they assume a typical glandular appearance and are low columnar or cuboidal. Often the tumor cells are small round discrete elements with very little protoplasm Such cells frequently retain their capacity for secreting mucus, so that the cell body is swollen and its nucleus displaced to the periphery, producing the typical signet ring appearance.

Metastatic Involvement of the Dura.—In none of the cases in the present series was it possible to find in the dura any lesion which seemed to represent the original focus of invasion. However, considering the nature of the lesions in the brain, one may reasonably assume that the dural metastases, like the encephalic ones, are vascular in origin and arise from focal involvement of some of the dural vessels. To describe the nature of these dural lesions adequately, one must briefly review the histologic structure of the dura. This membrane is composed of two indefinite layers of dense fibrous tissue. The bundles of connective tissue intertwine and are frequently separated by grooves or interspaces, the so-called lacunas. The inner surface of the dura is covered by a single layer of cuboid cells, which may be immediately on the dense fibrous dura or, as is more frequently the case, may be separated from the dura by a thin layer of loose connective tissue called the subepithelial layer. Blood vessels are very few within the dura. Most of the dural vessels are situated in two positions: A layer of vessels can be found in the midportion of the dura, between the two inseparable layers of collagenous fibers. The richest vascular network, however, is found in the delicate loose connective tissue that lines the innermost portion of the dura, the subepithelial layer. If one may assume that the neoplastic elements reach the dura through the blood stream, the vessels primarily involved are those within the subepithelial layers, for dural metastases

are most commonly found within this region. Once tumor cells have implanted themselves within this region, the spread may be either focal or diffuse.

(*a*) Focal Dural Tumors. These usually form discrete nodules within the dura. The neoplastic elements, once having become implanted, grow along the pathway of least resistance, which is toward the inner or arachnoid surface of the dura, since it is this region that is composed only of loose connective tissue and does not have the support of the heavy fibrous dura. The rapid proliferation of the tumor cells eventually results in the formation of a definite gross nodule protruding from the inner surface of the dura. As the neoplastic elements proliferate, changes occur within both the inner and the outer regions of the nodule. That part farthest from the dura usually undergoes necrosis and hemorrhage, with only a few remnants of the tumor cells remaining within the necrotic mass. In some cases most of the metastasis becomes necrotic, leaving only a thin rim of neoplastic tissue adjacent to the dura. Changes of an entirely different nature occur within the tumor tissue that lies adjacent to the dura. Capillaries and accompanying fibroblasts grow out from the dura and penetrate the neoplastic elements. The spindle-shaped fibroblasts are by far the most active elements and lay down many fine and coarse strands of collagen, many of which seem to merge with the underlying dura and form the basis of the adherence of the tumor to the pachymeninx. The collagenous elements ramify between the tumor cells, dividing them into tiny clumps. These fibroblastic elements eventually compress and obliterate many of the surrounding vessels, which no doubt accounts for a good deal of the distal necrosis.

Although the greatest part of the solitary dural tumor remains localized to the subepithelial layer, some of the cells do dissect between the heavy bundles of connective tissue and accumulate within some of the tissue spaces to form scattered isolated islands of neoplastic elements. More commonly the extension into the dura assumes a vascular nature. The neoplastic cells spread from the original focus within the subepithelial region along the perivascular spaces to the vessels within the midportion of the dura, which they then surround and even replace. Heavy bands of uninvolved dural tissue invariably separate the two vascular regions which are filled with metastases. Blood vessels are also present in the outermost or periosteal layer of the dura, and occasionally even these vessels become invaded by tumor cells through a perivascular spread.

(*b*) Diffuse Dural Lesions. The diffuse lesions also seem to arise through an embolic involvement of some of the subepithelial blood vessels. From here, however, the neoplastic elements, instead of proliferating to form a single nodule, spread longitudinally between the loose fibers of the subepithelial layer to establish numerous widespread

foci over the inner surface of the dura. The fibroblastic elements of this layer deposit collagenous fibers between the tumor cells, dividing them into tiny isolated clumps. This extensive fibroblastic proliferation produces marked thickening of the subepithelial region, which is eventually transformed into a heavy collagenous layer filled with tiny islands of tumor tissue. Some of the neoplastic elements also spread into the dura proper in a manner similar to that seen in the focal type of involvement.

Metastatic Involvement of the Spinal Cord.—Uncomplicated metastases in the substance of the spinal cord are extremely unusual. One such case was reported by Kolisko.[45] Lubarsch examined 19 cords in cases of carcinoma of different organs and found diffuse degeneration of the posterior and lateral columns in all. He was not sure whether this damage was secondary to the presence of a toxin or to cachexia.

The chief involvement of the cord in the cases of the present series was due to extension of the neoplastic elements caudally from the subarachnoid space of the cranial cavity. In 1 case there was an intramedullary lesion, but the destruction in the cord was so extensive and the tissues available for study so limited that no information could be obtained histologically concerning the evolution of this intramedullary lesion.

The involvement of the spinal subarachnoid space resembles in most details that already outlined for the leptomeningeal metastases. The neoplastic elements may be extremely numerous and frequently are deposited in irregular cords or nodules, many of which have a definite perivascular arrangement. Numerous collagenous fibers ramify between and around the tumor cells, even replacing many of the tumor elements, to result in a diffuse or focal obliteration of the subarachnoid space. The blood vessels show some endothelial proliferation. In none of the cases in this series was there complete occlusion of the vascular lumen, although such a process, if present, could very well produce extensive secondary changes in the cord. The spinal pia may be thickened and usually acts as a barrier to direct tumor invasion of the underlying parenchyma. When extension to the cord occurs, it is chiefly through the perivascular spaces of the vessels as they penetrate from the involved subarachnoid space. The neoplastic elements more commonly extend outward to involve the arachnoid and occasionally even the dura. In 1 case the tumor elements not only had destroyed the cord but had replaced all the covering membranes and spaces, so that the entire spinal canal was filled with the neoplastic tissue. None of the patients showed any degenerative changes in the cord elements.

The spinal rootlets may be invaded by tumor elements. Either some or all of the rootlets may be involved. Usually this invasion is limited to the interstitial elements of the rootlets rather than the nerve paren-

chyma. The tumor cells frequently surround the rootlets, forming dense collars about them. Some of the neoplastic elements may extend inward to replace not only the epineurium but also the perineurium. Even though the parenchyma is not invaded in such cases, degenerative alterations occur in it secondary to the compression of the rootlet. Occasionally all elements of the rootlets are replaced by the metastatic neoplasm.

Metastatic Involvement of the Sympathetic System.—This part of the nervous system does not usually receive adequate investigation because it is not routinely removed at autopsy. In none of the present cases was the sympathetic system available for study. However, during the course of a separate investigation, carried out in this laboratory by Dr. M. Schadewald, the lateral chain ganglions of the sympathetic system were studied routinely. In 1 case the sections revealed numerous tumor cells forming tiny nodules within the ganglions, often replacing and destroying many of the cells. The ganglion cells adjacent to these small tumor nodules were greatly altered, showing extensive chromatolysis, fragmentation and occasionally some swelling. The blood vessels within these ganglions were dilated, and many were partially filled with large irregular dark-staining tumor cells. In some areas the tumor cells had extended through the thin-walled vessels into the adjacent tissue.

The presence of tumor cells within the vessels and within the ganglions of the sympathetic system certainly lends added support to the belief that the spread of metastases to the nervous system is probably hematogenous. It also emphasizes the importance of including the sympathetic system in routine investigations of the nervous system.

SUMMARY

A clinicopathologic study of 114 tumors metastatic to the nervous system is reported; tissues were available from 92 for histologic investigation.

Tumors metastatic to the nervous system are probably much more common than is generally suspected. The number of tumors with such metastases will vary, depending on the thoroughness of the pathologic studies and the frequency with which autopsies are performed on persons dying of cancer.

The majority of intracranial metastases are probably hematogenous in origin. Numerous factors point toward such a spread: (*a*) the frequency of vascular lesions within the primary tumor; (*b*) the presence of neoplastic elements within the blood vessels of the brain; (*c*) the infarctions of the brain caused by tumor emboli; (*d*) the frequent distribution of the lesions in those areas of the brain receiving the greatest blood supply, i. e., the cortex and the subcortical regions; (*e*) the occasional distribution of lesions in those regions supplied by the

middle cerebral artery; (*f*) the occurrence of tumor elements within the choroid plexus; (*g*) the finding of tumor cells within the blood stream.

The most common primary sources of the metastases in the nervous system in this series of 114 cases were the lung, the breast, the gastro-intestinal tract and the kidney.

Metastatic tumors comprised 17.9 per cent of all intracranial neoplasms studied at the University of Minnesota.

Metastases occurred most frequently between the fifth and the seventh decades, primarily in the sixth decade of life.

Metastases in the nervous system do not give rise to any specific symptom complex but may produce symptoms of a widely disseminated nature. Generally, any patient in whom symptoms of an intracranial tumor develop rather rapidly in middle life or later should be carefully investigated for a possible metastatic lesion. Suggestive of metastatic involvement are meningeal signs or radicular pain, extreme wasting with a rapid decline, infrequency of signs of increased intracranial pressure with the exception of headache, and infrequency of papilledema.

In their gross appearance metastatic lesions of the brain are most variable and often resemble lesions of other categories. Grossly they can be divided into six different types: soft necrotic, gelatinous, granular, hemorrhagic, hard and melanotic.

Histologically, tumor cells can be seen within the arteries of the brain. These cells, by their growth, obliterate the vessels and produce the early neoplastic lesions.

After becoming implanted within the brain, the tumor cells begin to proliferate, and the growths assume numerous appearances, depending on their mode of spread and the nature of their cellular elements. Histologically they can be divided into seven types: predominantly epithelial, predominantly perivascular, encephalomalacic, gliotic, vascular, hemorrhagic and melanotic.

In most cases there is a remarkable resemblance between the primary lesion and the metastases in the nervous system.

Metastases, once established within the brain, may spread to other regions (1) by direct extension, (2) through the perivascular spaces of the adjacent vessels or (3) by breaking through into the ventricles or subarachnoid spaces.

Cerebral or cerebellar metastases often produce softening of the surrounding brain tissue but usually stimulate little or no glial reaction.

Toxic changes are not observed in tissues not directly involved by the tumor elements. Remote brain changes were not seen.

Meningeal metastases may be of a diffuse or a nodular type. When the neoplastic elements secondarily invade the brain, it is usually along the perivascular spaces of the meningeal vessels as they penetrate into the underlying cerebral tissue.

CULTIVATION OF HUMAN LEUKEMIC LEUKOCYTES ON THE CHORIOALLANTOIC MEMBRANE OF THE CHICKEN EGG

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This paper deals with cultivation of human leukemic leukocytes on the chorioallantoic membrane of the chick embryo.

METHODS AND MATERIALS

Blood leukocytes from 14 children with acute leukemia and 2 adults with chronic myeloid leukemia were cultured.

The leukocytes were prepared for explantation in a clot as follows: Venous blood was drawn into a saline solution of heparin to prevent coagulation during centrifugation, the plasma removed and the buffy coat of leukocytes coagulated by the addition of a few drops of chick embryonic extract and rabbit plasma; the clot was then removed from the underlying layer of erythrocytes and minced into small bits in Tyrode's solution; these bits were transferred to the chorioallantoic membrane of the embryo with as little trauma as possible.

In experiments 6, 7, 8, 15 and 16 a drop of cells from the buffy coat was pipetted directly onto the membrane in a pool.

Fertile eggs were incubated at 39.5 C. for nine to eleven days; a window 1.0 cm. square was then made in the shell with a dental drill, exposing the chorioallantoic membrane. The leukocytes were placed on the membrane, and the window was rimmed with petrolatum and sealed with a cover slip. The eggs were then reincubated for a variable number of days. Membranes and embryos were examined for gross evidence of change, then fixed in Zenker's formaldehyde solution,[1] sectioned and stained in hematoxylin and eosin.

The results of the experiments are summarized in the accompanying table.

RESULTS

Histology of the Chorioallantoic Membrane Inoculated with Normal Blood Leukocytes.—The typical changes produced in the chorioallantoic

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From the Department of Hematology of the Children's Memorial Hospital, Chicago.

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1. This is Zenker's solution prepared with solution of formaldehyde U. S. P. instead of acetic acid.

Details of Cultures of Leukemic Cells on Chorioallantoic Membrane

In each case broth cultures of the membrane remained sterile. No embryos were allowed to hatch and there was no evidence of leukosis in any embryo.

Experiment	Age of Patient	Diagnosis	Total White Blood Cell Count on Day of Culture	Percentage of Leukemic Cells (Stem Cells)	Embryos				Histologic Observations	
					Period of Incubation When Inoculated, Days	Period of Incubation When Fixed for Study, Days	Embryos Inoculated	Embryos Fixed	Fate of Explant on Membrane	Evidence of Leukosis in Hatched Chicks
1	15 mo.	Chloroma	54,000	14	9	10-19	22	10	Absorbed	
2	3 yr.	Acute leukemia	29,000	96	9	11	10	1	Absorbed	
3	3 yr.	Acute leukemia	4,000	94	8	10	8	2	Absorbed	
4	4 yr.	Acute leukemia	27,000	76	12	18	5	5	Absorbed	
5	8 yr.	Acute leukemia	300,000	80	10	13, 14	12	4	Absorbed	
6	2 mo.	Acute leukemia	50,000	96	9	15, 17	11	7	Enlargement and growth	
7	Adult	Chronic myeloid leukemia	200,000	....	15	19	15	4	Enlargement and growth	
8	Adult	Chronic myeloid leukemia	150,000	....	9	15	10	2	Absorbed	
9	4 yr.	Subacute lymphatic leukemia	50,000	99	9	14, 18	30	5	Enlargement and growth	
10	5 yr.	Acute leukemia	Bone marrow	99	5	15	16	1	Absorbed	None leukemic after 5 mo.
11	10 yr.	Acute leukemia	4,500	98	9	17, 18	9	3	Enlargement and growth	None leukemic after 5 mo.
12	3 yr.	Acute leukemia	37,000	78	9	13	13	3	Absorbed	None leukemic
13	5 yr.	Subacute leukemia	5,000	16	10	19	13	5	Absorbed	
14	4 yr.	Acute leukemia	50,000	90	9	20, 23	17	3	Absorbed	None leukemic; died on 6th day
15	5 yr.	Acute leukemia	10,000	....	9	13, 14, 15	18	5	Absorbed	None leukemic after 5 mo.
16	6 yr.	Acute leukemia	30,000	....	13	20	18	2	Enlargement and growth	None leukemic at 4 mo.

membrane by explantation of a clot of normal blood leukocytes were as follows:

Within twenty-four to thirty-six hours after explantation, the explant was in most instances adherent to the membrane, which appeared grossly somewhat thickened and edematous. Within forty-eight hours, focal opacities were frequently visible, and a rich network of small capillaries was demonstrable in stained whole mount preparations. Sections through the explant and adjacent membrane showed migration of a few ameboid leukocytes from the periphery of the explant; the majority of the cells within the explant were pyknotic. Under the explant was a layer of serum or tissue fluid which cemented it to the ectoderm; this was often flattened but never necrotic. Beneath and around the explant, budding capillaries and sinusoids were distended with chick blood cells. Lymphocytes and granulocytes were found in the position of ameboid migration through the vascular endothelium and were gathered in dense accumulations about the region of the explant. These cellular aggregations corresponded to the focal areas of opacity visible grossly; they consisted of lymphocytes, eosinophils and a few heterophilic granulocytes in various stages of maturity. After four days, all of the cells within the explant were pyknotic. Polyblasts had phagocytosed debris of the disintegrating leukocytes; smaller polyblasts containing ingested nuclear material were visible in the capillaries and sinusoids, demonstrating the method of transportation of the foreign substance from the membrane by way of the circulation into the body of the embryo.

Histology of the Chorioallantoic Membrane Inoculated with Leukemic Cells.—In eleven of sixteen experiments the changes noted in the membranes inoculated wtih leukemic cells were not unlike those described in the membranes inoculated with normal blood leukocytes. The cellular reaction consisted of lymphocytes, polymorphonuclear leukocytes and phagocytes, which removed the explanted cells within two to four days after explantation.

In five of sixteen experiments, however, the cellular reaction of the membrane to the explant was striking in degree and quality. In each instance the explanted cells multiplied by mitotic division so that gross enlargement of the explant was apparent. The explant was embedded in the mesenchyme and covered by a thickened layer of ectoderm (fig. 1 *A*). The ectodermal cells at the side of the explant were enlarged and vacuolated, and many contained the red intracytoplasmic formations that suggest inclusion bodies. The ectodermal layer below the explant was flattened and invaded by large polyblasts, which surrounded it and walled it off from the underlying mesenchyme. While the center of the explant was composed of disintegrating cells in various stages of karyolysis, the peripheral zone was made up of enlarged and ameboid

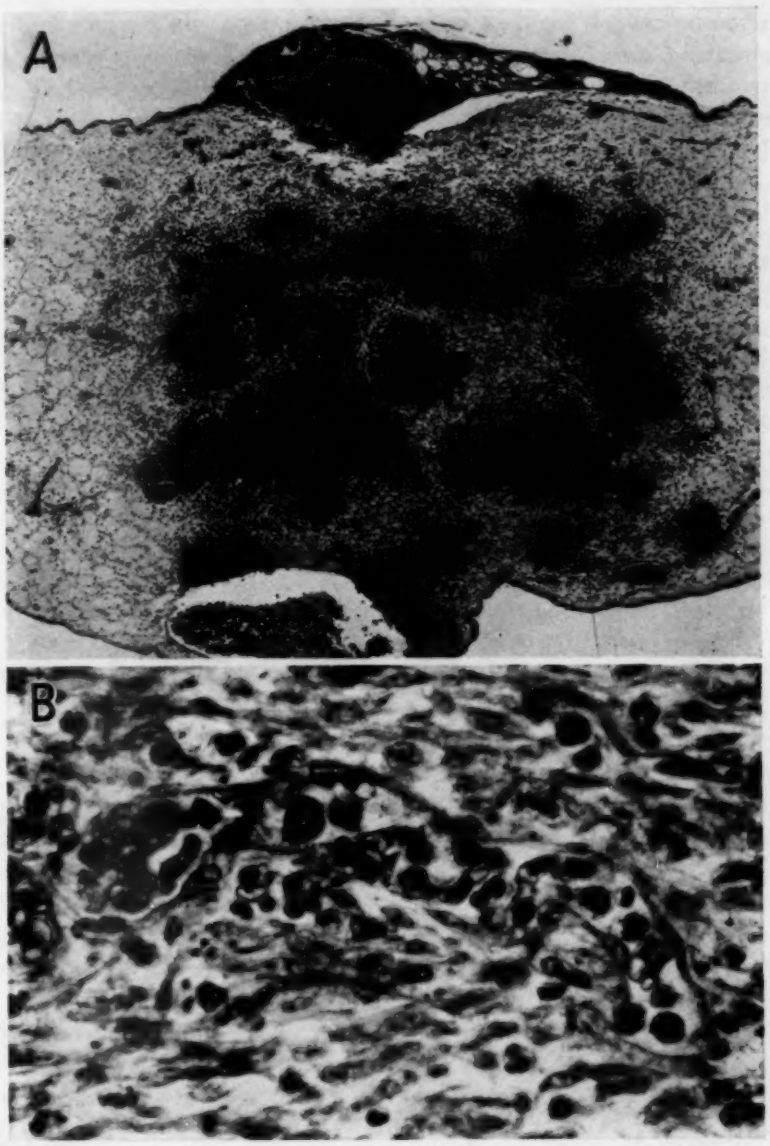

Fig. 1.—*A*, chorioallantoic membrane nine days after it had been inoculated with a clot of leukocytes in case 9 (subacute lymphatic leukemia); × 45. The explant is embedded beneath the ectoderm, which is thickened and proliferated. The central zone is pyknotic, and the peripheral zone is partially walled off by ectodermal cells and polyblasts. Below the explant is a dense aggregation of cells within the mesenchyme, the details of which are seen in *B*.

B, detail of the cellular constituents of the membrane shown in *A*; oil immersion field; × 800. Note the viable explanted leukemic cells, the pyknotic explanted leukemic cells, the capillary containing hemocytoblasts and polyblasts of embryonal origin, which are removing cell debris, the fibroblasts and the polyblasts.

leukocytes, which could be traced migrating from the explant into the underlying mesenchyme. The dense aggregates of cells beneath the explant (fig. 1 *B*) were composed of a mixture of the ameboid and disintegrating explanted cells and inflammatory cells of membrane origin. The latter cells were predominantly myelocytes with the coarse granula-

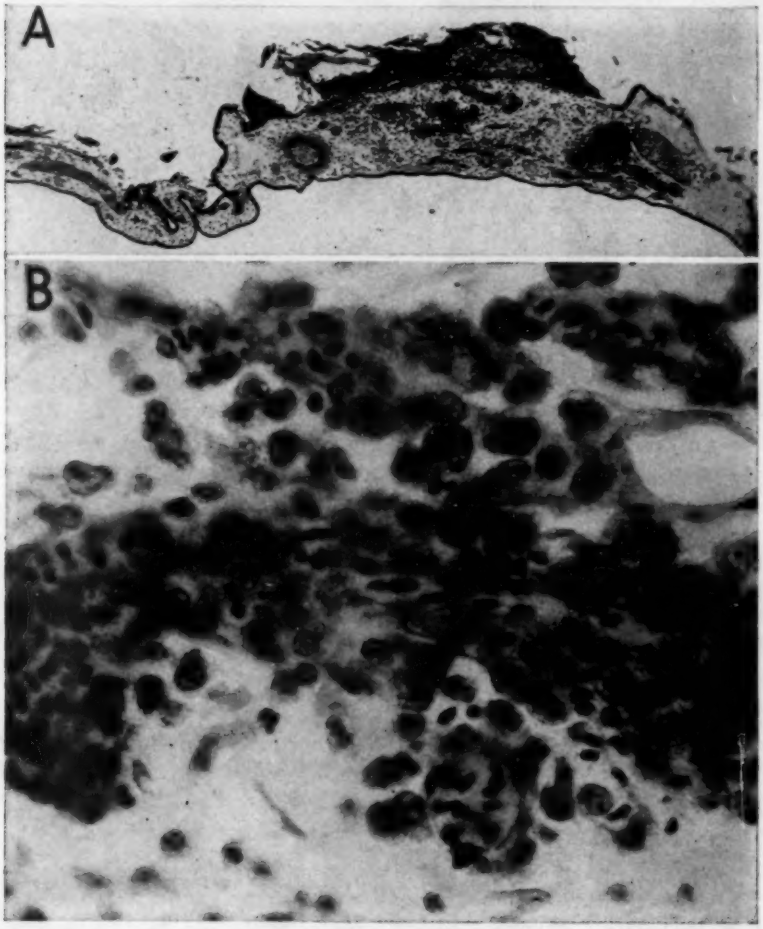

Fig. 2.—*A*, chorioallantoic membrane nine days after it had been inoculated with a clot of blood leukocytes in case 11 (acute stem cell leukemia); × 45. The explant was visibly enlarged, and the section shows the cellular reaction in the mesenchymal layer.

B, detail of the cellular constituents of the membrane shown in *A*; oil immersion field; × 800. Note the myelocytes within the coarse granulation of chick leukocytes and the intravascular erythrocytes.

tion characteristic of chick granulocytes, and phagocytic polyblasts. In figure 2 *A*, disintegrating forms which have not been phagocytosed are

seen throughout the membrane, indicating death of the explanted cells after ameboid migration. A few hypertrophied nongranular cells suggest the presence of viable explanted cells. These, however, could not be differentiated from lymphocytes of membrane origin; no cells with the fine neutrophilic granulation of human myelocytes were seen, so that maturation of the explanted stem cells could not be assumed to have occurred.

Histologic Changes in the Embryo.—In none of the embryos inoculated with leukemic blood leukocytes were changes suggestive of leukosis observed. None of the criteria of leukotic change, such as consistent gross hypertrophy of the spleen, stimulation of embryonal mesenchyme or intravascular hemocytoblastosis was observed. The presence of degenerating leukocytes within the sinusoids of the liver and among perivascular cells was evidence of transportation of cells from the explant into the embryo, but no evidence was found that living cells were likewise carried into the embryo, there to set up metastatic foci of cell formation. No consistent findings characteristic of bacterial growth were present; many of the embryos were sluggish and failed to develop to the normal size, while others appeared normal. Common findings among the few that failed to develop normally were atrophy of the liver parenchyma and enlargement of the spleen and hyperplasia of the follicles.

COMMENT

The most significant features of the findings described are the ability of leukemic leukocytes to survive under ideal conditions on the chorioallantoic membrane for a limited period, and the intense myelocytic reaction produced in the membrane by these cells when they continued to live in this artificial medium. While these observations suggest that leukemic cells stimulate a myelocytic response in contradistinction to the multicellular response induced by normal leukocytes and other foreign substances placed on the membrane, such a conclusion must be guarded. It seems more likely that two well known characteristics of leukemic leukocytes, apparent in vitro as well as in vivo, i. e., rapid cell division and active ameboid motion, explain their ability to invade the membrane before polyblasts successfully wall off the explant and block migration of the explanted cells. It is probable that the immaturity of cells of membrane origin, produced because of the presence of leukemic cells within the mesenchymal layer of the membrane, is a measure of the intensity of the cellular reaction and that it is not a specific myelocytic response to the leukemic leukocytes per se.

The lesions in the ectoderm were those commonly found in membranes inoculated with other foreign substances and also in virus infec-

tions of the membrane: thickening and flattening, keratinization and pearl formation, and the presence of intracytoplasmic inclusion-like bodies within enlarged ectodermal cells. While these lesions have been interpreted variously and have been described by many observers [2] as evidence of virus infections specifically, they have also been observed in membranes inoculated with sterile broth or salt solution [3] and must therefore be interpreted with caution. If these changes are to be interpreted as evidence of virus infections of the membrane, the presence of the virus must be confirmed either by animal passage or by characteristic reactions in the embryo.[4] In these experiments no evidence was obtained that these lesions in the membrane were accompanied by pathologic changes common to leukosis in the embryo or in any chicks hatched from the eggs inoculated with leukemic cells. It is then apparent that, provided the embryo survived the period of myelocytic stimulation induced by the explantation of leukemic cells, no permanent effect on the organs of hemopoiesis was maintained.

SUMMARY

Normal blood leukocytes and leukocytes from 16 patients with leukemia were explanted on the chorioallantoic membranes of developing eggs.

Normal blood leukocytes produced a cellular reaction of lymphocytes, polyblasts and polymorphonuclear granulocytes within the membrane, which migrated from the blood vessels to the region of the explant. Survival of the leukocytes within the explant was not observed. Polyblasts removed the cellular debris and carried the disintegrating cells into the circulation of the embryo. A few ameboid lymphocytes and polymorphonuclear leukocytes migrated from the explant into the membrane, died and were subsequently removed by polyblasts.

Leukemic blood leukocytes similarly explanted either died promptly and were removed by inflammatory cells of the membrane or survived for a short period, in which instance gross enlargement of the explant was apparent. Multiplication of the cells occurred, and enlarged ameboid forms migrated into the mesenchyme of the membrane, where they induced an intense myelocytic reaction among cells of membrane origin.

Disintegrated explanted cells were transported into the body of the embryo, but cellular aggregations suggestive of leukemic infiltration were not observed in the organs of the embryo.

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None of the chicks inoculated as embryos with leukemic cells or plasma showed leukosis after hatching.

The chorioallantoic membrane of the developing egg provides a medium which under suitable conditions permits human leukocytes to continue to grow for a short period. Evidence was not obtained in these experiments that a leukemic change could be produced in the embryo or the chick by inoculation of the membrane with leukemic leukocytes.

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Case Reports

MULTIPLE MYELOMA WITH UNUSUAL VISCERAL INVOLVEMENT

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Extraskeletal lesions in multiple myeloma are usually the result of direct extension of the disease process through destroyed bone. Less common is the involvement of distant visceral organs. The most frequent sites of this type of infiltration are the lymph nodes, liver and spleen, in the order mentioned.[1] However, almost any part of the body may participate. Nodular infiltrations have been found in the kidneys,[2] lungs,[3] heart,[4] skin and subcutaneous tissue,[5] tonsils,[6] thyroid,[7] testes,[8] ovaries,[9] pleura,[5e] gastrointestinal tract,[10] uterus,[5e] adrenals[11] and dura.[2b] In most cases involvement of the lymph nodes, liver, spleen or kidneys is found only on microscopic examination. Grossly visible nodules are almost as rare in these organs as elsewhere. Visceral involvement is of interest not only because of its rarity but also because of the important bearing it has on the question of the nature of the disease. For this reason, the following case is noteworthy.

REPORT OF A CASE

A 60 year old white man, a pharmacist, first entered the hospital (medical service of Dr. Eli Moschcowitz) Sept. 9, 1941. His chief complaints were earache for ten days and drowsiness for six months. His mother had died of "nephritis." The past history of the patient was of no significance. He stated that his health had been good until six months before admission, when increasing somnolence had been noted.

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1. Geschickter, C. F., and Copeland, M. M.: Arch. Surg. **16**:807, 1928.

2. (*a*) Morse, P. F.: J. Cancer Research **5**:345, 1920. (*b*) Carlisle, V.: South African M. J. **12**:298, 1938. (*c*) Stewart, A.: Quart. J. Med. **7**:211, 1938.

3. (*a*) Cabot case 22502, New England J. Med. **215**:1133, 1936. (*b*) Zäh, K.: Virchows Arch. f. path. Anat. **283**:310, 1932. Carlisle.[2b]

4. Piney, A., and Riach, J. S.: Folia haemat. **46**:37, 1931. Morse.[2a] Carlisle.[2b]

5. (*a*) Kreibich, C.: Folia haemat. **18**:94, 1914. (*b*) Duvoir, M.: Bull. et mém. Soc. méd. d. hôp. de Paris **54**:687, 1938. (*c*) Loubat: Bordeaux chir. **9**:36, 1938. (*d*) Christian, H. A.: J. Exper. Med. **9**:325, 1907. (*e*) Nicholls, A. G.: Canad. M. A. J. **17**:301, 1927. Piney and Riach.[4]

6. Jackson, H.; Parker, F., and Bethea, J. M.: Am. J. M. Sc. **181**:169, 1931. Schütz, H.: Deutsches Arch. f. klin. Med. **113**:441, 1914.

7. Batts, M., Jr.: Arch. Surg. **39**:807, 1939.

8. Ulrich, H.: Arch. Int. Med. **64**:994, 1939.

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10. Carlisle.[2b] Nicholls.[5e]

11. Stewart.[2c] Nicholls.[5e]

June 8, 1941, he entered another hospital, complaining of weakness. There the physical findings included puffiness of the face, pallor and drowsiness. The blood pressure was 120 systolic and 90 diastolic. The urine showed a trace of albumin, a few hyaline and granular casts and 10 to 15 white blood cells per high power field. The blood urea nitrogen was 47.8 mg. per hundred cubic centimeters. The hemoglobin content was 46 per cent, the red blood cell count 3,650,000 and the white blood cell count 8,600 with 76 per cent neutrophils. It was noted that "it was impossible to give this patient more than one transfusion, because he was an atypical type IV (Moss) [O]. His blood formed rouleaux with five attempted donors." The blood pressure rose to 158 systolic and 84 diastolic. Azotemia first deepened, then diminished, and the patient was discharged July 3. The diagnosis was "chronic glomerulonephritis."

After he left the hospital, vomiting and dizziness supervened. Ten days before admission to the Mount Sinai Hospital, following a cold, pain developed in the left ear, to be followed by a discharge.

The patient appeared adequately nourished. The heart was of normal size. A soft systolic murmur was heard at the apex. The blood pressure was 170 systolic and 100 diastolic. The lungs were clear. The liver and the spleen were moderately enlarged. The fundi showed thin, tortuous arteries and occasional linear hemorrhages. An anterior perforation was found in the left ear drum, through which came a pulsating purulent discharge. The impression on admission was "chronic glomerulonephritis and acute purulent otitis media."

The hemoglobin content was 43 per cent. The red blood cells numbered 2,270,000 per cubic millimeter; the white blood cells, 6,500, with 51 per cent segmented and 11 per cent nonsegmented neutrophils, 1 per cent metamyelocytes, 31 per cent lymphocytes and 1 per cent eosinophils. The Wassermann test was negative. The erythrocyte sedimentation rate (Linzenmeier) was 18 mm. in ten minutes. During routine urinalysis, Bence Jones protein was found. This was present in moderate amounts on several occasions. Albumin was present in the urine—a very faint trace; dextrose was absent; microscopic examination showed occasional red and white cells. During a concentration test the specific gravity varied between 1.008 and 1.011, but that of one casual specimen reached 1.026. The blood urea nitrogen amounted to 55 mg. per hundred cubic centimeters, blood calcium to 9 mg. and phosphorus to 5.5 mg. Blood phosphatase amounted to 13 King-Armstrong units; albumin, to 3.6 per cent; globulin, to 5.1 per cent; total protein, to 8.7 per cent; carbon dioxide content, to 45.3 volumes per cent. Staphylococcus aureus was cultured from the aural discharge. An electrocardiogram revealed no definite abnormalities. Roentgen examination of the skeleton showed slight general thickening of the bones of the calvarium, which had a rather peculiar mottled appearance. The facial bones and the cervical vertebrae also showed a similar peculiar decalcified and mottled picture. The remainder of the vertebral column was obscured by intestinal gas. In the right innominate bone there was an irregular area of rarefaction. The bones of the entire pelvis showed peculiar disorganization.

After the disclosure of Bence Jones proteinuria, aspiration of sternal marrow was performed; the marrow showed "many plasma cells—typical of multiple myeloma." The roentgen changes were thought to be consistent with this diagnosis, although not characteristic. A congo red test showed tissue absorption of 40 per cent after one hour.

Treatment consisted of blood transfusion and forcing of fluids. The temperature was normal throughout. There appeared to be no change in the patient's condition until the twelfth hospital day, when he died suddenly and unexpectedly.

Postmortem Observations.—Only the pertinent findings are recorded here. The body was that of a well nourished and well developed white man of middle age.

There was no generalized lymphadenopathy, no jaundice, no edema. Neither the abdomen nor the chest contained any excess of free fluid. There were fairly dense adhesions at the apex of the left lung.

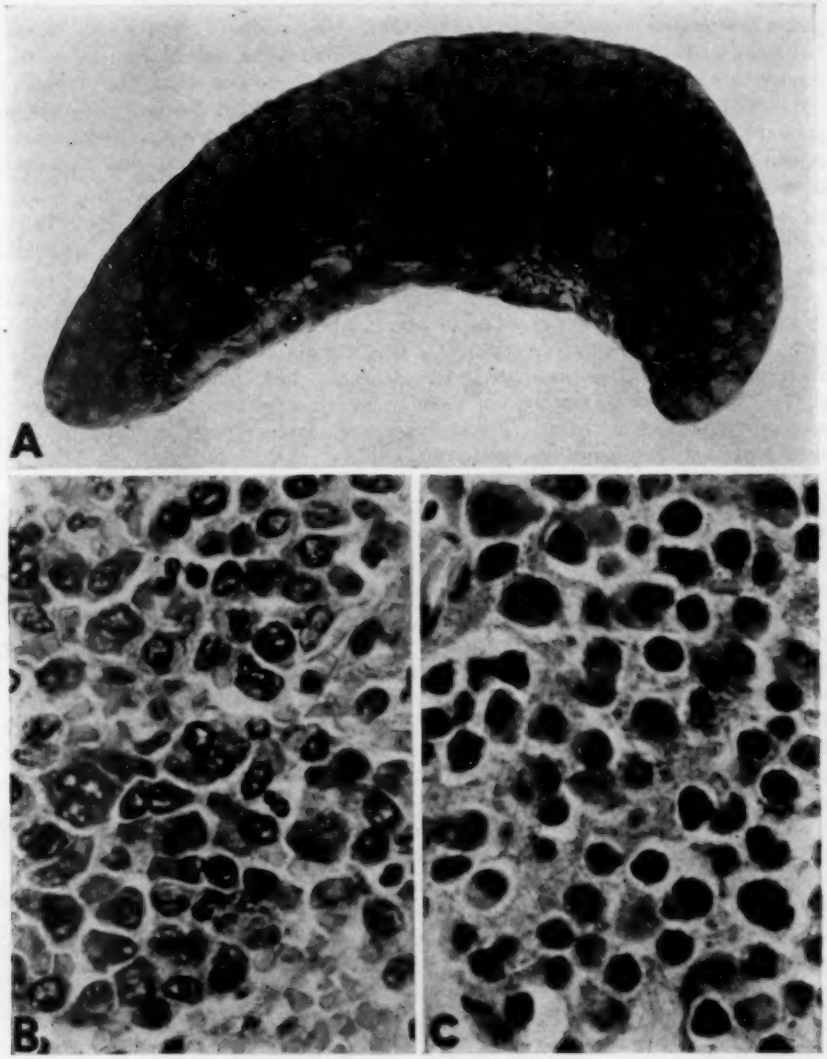

Fig. 1.—*A*, cut surface of the spleen after Kaiserling fixation, showing tumor-like infiltrations. *B*, high power view of an area of infiltration in the spleen. *C*, myeloma cells in the bone marrow.

(*a*) Spleen: The spleen presented the most striking picture (fig. 1 *A*). It was greatly enlarged, weighing 650 Gm. Through the thin capsule, innumerable white nodules could be seen. These varied in size from that of a pinhead to 1 cm. in

diameter and were firm in consistency. On section they appeared as whitish pink, very finely granular areas which comprised the greater part of the splenic tissue. The largest of the areas had soft necrotic centers. Thus, the splenic structure was conspicuously disturbed. Occasionally, however, grayish white malpighian corpuscles could be recognized within the remaining splenic pulp. The splenic artery and vein were destroyed in removing the organs.

Microscopic examination showed the greater part of the splenic parenchyma replaced by large and small nests of abnormal cells (fig. 1*B*). These cells were round or oval, assuming a polygonal shape only when clumped together, and had a distinct cell membrane. They were two to three times the size of red blood cells. In hematoxylin-eosin preparations the cytoplasm was homogeneous and deep reddish purple. Rarely, a small perinuclear halo was present. The nucleus was about the size of a red cell or larger and round or oval. The nuclear membrane was distinct. Many larger cells had two nuclei, usually at opposite poles, and some cells had as many as four. The nuclei varied in staining qualities and in position within the cell. The predominant type was slightly eccentric, stained deeply and showed clumplike arrangement of chromatin, mainly around the circumference of the nucleus but also nearer the center. Frequently a small nucleolus was present. Other cells, however, had a centrally located nucleus, which was pale staining and the chromatin of which was in the form of delicate filaments scattered throughout the nucleus. These showed a prominent nucleolus. In the latter type of cell, the cytoplasm was less abundant, forming a comparatively narrow rim around the nucleus. Rare mitoses were seen. The peroxidase reaction was negative.

In hematoxylin-eosin preparations the predominant cell on superficial examination could be readily mistaken for a plasma cell, chiefly because of the eccentric position of the nucleus, the basophilic cytoplasm and the occasional perinuclear halo. There were several differences, however, which were brought out particularly by special stains—e. g., the Unna-Pappenheim methyl green–pyronine stain and the Heidenhain modification of Mallory's aniline blue stain: 1. In general, the cells were larger than plasma cells. 2. The perinuclear halo was only rarely seen. 3. The cytoplasm did not stain as intensely with pyronine. 4. The nuclear chromatin did not have the typical coarse spoke wheel arrangement but was more delicate and was irregularly distributed. 5. A distinct nucleolus was present in almost every cell, best seen in the Heidenhain or the Giemsa stain. In methyl green–pyronine preparations the nucleolus appeared pink, in contrast to the greenish blue chromatin.

The groups of these cells in the spleen were not sharply circumscribed but infiltrated the surrounding tissue. Mallory's stain revealed sparse delicate connective tissue stroma in the involved areas. There were also scattered vascular channels. The intervening red pulp was markedly congested and contained numerous granules of golden brown iron pigment both within and without the cell. Even in these areas the pathologic cells could be found, either singly or in small groups. The malpighian corpuscles were small but could be identified even in the solidly infiltrated areas. The capsule was slightly thinned, especially directly over the nodules. There was a greater distance between the trabeculae than normally.

(*b*) Liver: The liver was of normal size, weighing 1,500 Gm. The surface showed numerous irregular, more or less linear, depressed scars. Numerous sharply circumscribed pinpoint-sized white nodules were seen on the peritoneal and cut surfaces of the liver and occasionally under the intima of the branches of the portal vein. The structural appearance of the liver was otherwise normal.

On microscopic examination the capsule was thin, and the lobular formation of the liver was well preserved. There were numerous collections of pathologic cells, some small, but others forming macroscopically visible nodules. The latter were found chiefly in the periportal fields (fig. 2*A*), although many of these fields were

uninvolved. Smaller groups and single cells were seen in the sinusoids and occasionally about the central veins (fig. 2*B*). Heavily staining granular material (coagulated protein) was found in the blood vessels.

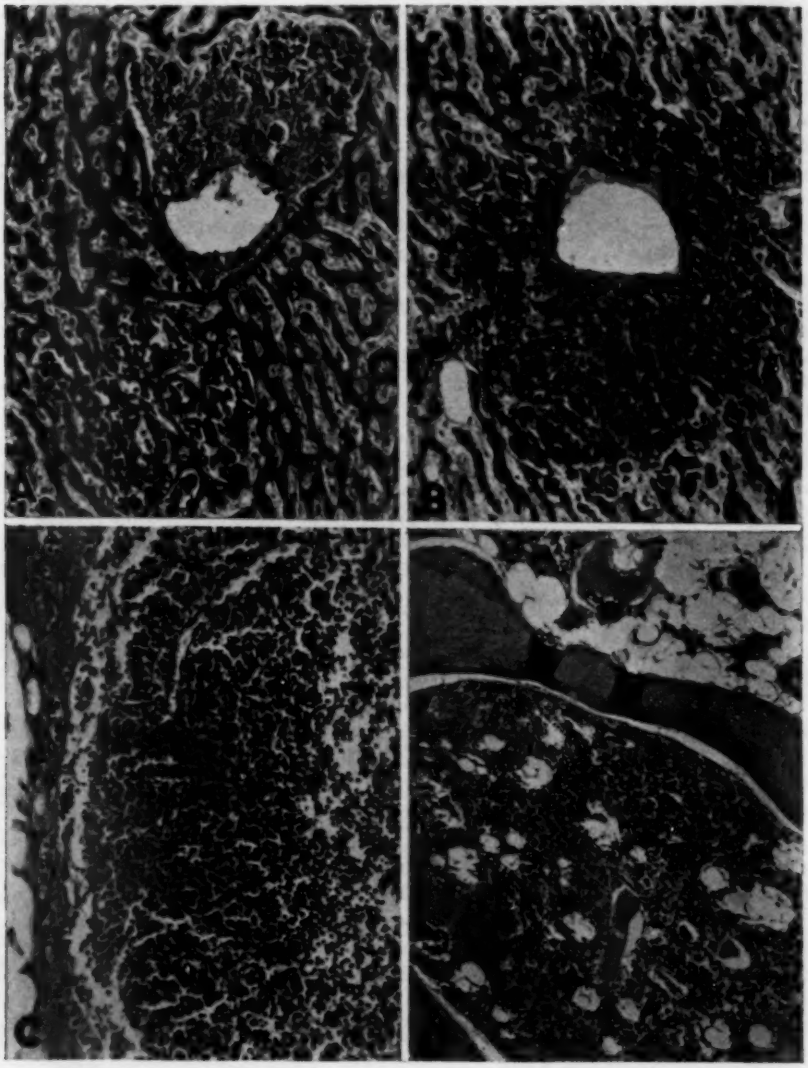

Fig. 2.—*A*, liver, demonstrating infiltration of myeloma cells in portal areas and sinusoids. *B*, infiltration around the central vein in the liver. *C*, lymph node showing a nodular area of infiltration in a subcapsular sinusoid. *D*, bone marrow. Most of the cells here shown are myeloma cells. Areas of fatty marrow and of normal cellular marrow are also seen.

(*c*) Lymph Nodes: Numerous anthracotic soft lymph nodes were found in the hilar region of the lungs. There were several enlarged soft peripancreatic, portal

and periaortic nodes, the largest measuring 3 cm. in length. On section they were of homogeneous pale structure, with circumscribed small paler areas at the periphery. Numerous enlarged soft nodes were also found about the lower end of the esophagus. The mesenteric nodes were slightly enlarged. The subcutaneous nodes did not seem to be enlarged; none was removed for study.

Microscopically, the peripancreatic, portal, periesophageal and periaortic lymph nodes were infiltrated by the same cells which prevailed within the spleen. The mesenteric nodes which were removed were not involved. In the smaller nodes, the pathologic cells formed flat nodules, not sharply circumscribed, in the subcapsular sinusoids (fig. 2 *C*). In some areas they extended along the septums, toward the medulla. In the larger nodes these cells were scattered throughout the parenchyma, singly or in groups, frequently arranged around lymph follicles.

(*d*) Lumbar Vertebra: Only several fragments of a lumbar vertebra were removed for examination. Because of the nature of the permission, no other bones could be examined. In the vertebral body there appeared to be small irregular defects, where the trabeculation was absent. No distinct infiltrations could be seen, however. The marrow appeared cellular.

Microscopically, the bony trabeculae were for the most part well preserved. Despite the presence of considerable fat, the marrow was very cellular. Cells identical with those previously described were seen to infiltrate the marrow, lying between the normal cells and occasionally forming small compact nodules (fig. 2 *D*). The nuclei of these cells were more compact than those found in the spleen (fig. 1 *C*). The resemblance to plasma cells was therefore more striking. Areas of uninvolved marrow tissue were present. A considerable amount of golden brown iron pigment was found. In some areas large amounts of pink-staining coagulated protein were seen.

(*e*) Kidneys: The kidneys were slightly enlarged and together weighed 320 Gm. The capsule stripped with difficulty, although it was thin. The surface of the kidneys was smooth and was pale and mottled purple. After fixation, irregular pits were seen on the surface. On section the parenchyma appeared somewhat parboiled. The differentiation of cortex from medulla was not as sharp as usual. Tan streaks and dots were irregularly scattered through the cortex and medulla. The glomeruli were seen as tiny red dots. There were hemorrhages in the pelves. A moderate amount of grumous red material was present in the calices.

On microscopic examination, small scattered scars were observed beneath the capsule, and occasionally deeper in the parenchyma, containing hyalinized glomeruli and a considerable amount of lymphocytic infiltration. There was considerable interstitial edema with increase in fibrous tissue. The glomeruli outside the scarred areas showed little change except for slight dilatation of Bowman's space, which occasionally contained coagulated protein. Many of the convoluted tubules were dilated. They contained loose, and occasionally compact, granular pink-staining material. The cells were frequently flattened, and their outline was not sharp. The cytoplasm contained large amounts of bright pink granular material. In Heidenhain's azocarmine preparation these granules stained bright orange-red. The nuclei were well stained. The collecting tubules were likewise dilated, and many of them were plugged by casts composed of the same deep pink granular material. Giant cells were absent. There was no infiltration by pathologic cells or amyloid. The larger arteries showed mild sclerotic changes, and many contained coagulated protein.

(*f*) Other Organs: The pathologic findings included a patent foramen ovale and slight coronary sclerosis with focal myofibrosis in the heart. The lungs showed areas of atelectasis and edema. A calcified primary tuberculous lesion was found

in the lower lobe of the right lung. The adrenal medulla showed areas of fibrosis and of round cell infiltration around the large veins. The cortex was very rich in lipoid. There were also areas of fibrosis in the periadrenal tissues. A pea-sized adenomyoma was found in the upper part of the ileum.

COMMENT

Several features of this case are worthy of notice. The correct clinical diagnosis was originally not made because of the lack of symptoms referable to the skeleton. In retrospect, hyperglobulinemia might have been suspected when the tendency to rouleaux formation was noted in the blood.[12] The correct diagnosis was arrived at only after the identification of Bence Jones protein in a routine specimen of urine and was confirmed by examination of aspirated sternal marrow. The changes in the bones as seen in roentgen films were reported as not typical of multiple myeloma. At autopsy, the portion of vertebra examined showed a more diffuse type of infiltration than is usually found, with comparatively little destruction of bone. Because of the limitations of the autopsy, however, it is difficult to draw any definite conclusions from these skeletal findings. The kidneys were characteristic of the entity which is coming to be known as "myeloma kidney." In addition to the blockage of part of the collecting tubule system by deep-staining casts, there was eosinophilic globular material in the epithelial cells of the convoluted tubules, which may be an indication of tubular implication by Bence Jones protein. Interstitial edema was striking.

Of particular interest was a most extensive nodular involvement of the spleen, most resembling that seen occasionally in lymphosarcoma. There was also involvement of the liver and the lymph nodes, although this was less striking.

A review of the literature reveals only 6 cases of multiple myeloma with extensive splenic infiltrations. Of these, 2 showed in addition to splenic myelomatosis widespread infiltration of other viscera. The case reported by Norris [13] (that of a boy of 16) presented widespread nodular infiltrations of the liver, thyroid, heart, pleura, thymus, adrenals, kidneys and lymph nodes. The spleen weighed 1,080 Gm. and was thickly studded with tumor nodules up to 5 mm. in diameter. The case was reported as a "systemic sarcoma of myelogenous origin." Except for the presence of numerous mitoses, the cells as described seem fairly characteristic of the usual type resembling plasma cells. Occasional nodules contained erythroblasts.

Sasaki's [14] patient, a 75 year old man, had small nodules in the skin, omentum, lungs, liver, spleen, adrenals and lymph nodes in addition to typical bone involvement. The author considered the cells in that case to be of the myeloblastic type. From his description, the cells seem similar to those in the present case except for an occasional positive peroxidase reaction.

Osgood and Hunter [15] reported a case of "plasma cell leukemia" in a man of 49. Autopsy showed an enlarged spleen in which circumscribed but confluent whitish

12. Foord, A. G., and Randall, L.: Am. J. Clin. Path. **5**:532, 1935.
13. Norris, C.: Proc. New York Path. Soc. **6**:128, 1906.
14. Sasaki, K.: Gann **33**:171, 1939.
15. Osgood, E. E., and Hunter, W. C.: Folia haemat. **52**:369, 1934.

areas were present throughout. Microscopically, almost the entire red and white pulp was replaced by "plasma cell" elements. The liver and lymph nodes showed microscopic involvement. The blood contained 24,200 white blood cells per cubic millimeter, with 54 per cent "plasma cells."

Shortly before Rustizky [16] first recognized multiple myeloma as a specific disease of bone marrow, Arnold [17] reported a case which he termed one of "primary myelogenous sarcoma of the skull bones," which very probably falls into the category of multiple myeloma. The patient was a man, aged 49. The duration of the disease was approximately eight months. There was tumor formation in the skull, the ribs and the clavicle. Both the liver and the spleen showed discrete pink nodules varying in size from that of a lentil to that of a walnut. The liver was of normal size, but the spleen was enlarged. The cervical and axillary lymph nodes were also invaded. The cells were large and round, occasionally polygonal, with large finely granular nuclei. There was little supporting stroma, but a considerable number of blood vessels and areas of hemorrhage were present. The kidneys were large, mottled, yellowish white and cloudy. A microscopic examination of the kidneys was not reported.

Reach [18] described the spleen in a case of multiple myeloma as showing numerous small grayish white nodules, rather sharply circumscribed. Histologically, the nodules in the spleen and in the bone marrow were composed of "round lymphoid cells with a large amount of cytoplasm."

The case of Slavens [19] possibly also falls into the present group. The patient was a boy 5 years old at the time of death. The duration of the disease was ten months. Bence Jones protein was absent from the urine. At postmortem examination there was widespread destruction of bones with diffuse and occasionally nodular infiltration of the bone marrow. The spleen "weighed 325 Gm. (normal, 53 Gm.). Its consistency was increased, and its color was grayish pink. The capsule was smooth and glistening. The cut surface revealed the same color, with grayish portions consisting of indefinitely small nodules. Normal malpighian markings and trabeculations were replaced by the grayish-pink transformation. No definite regions of tumor were found."

Microscopically, the marrow was infiltrated in a cordlike fashion without obliteration of fat tissue. "In some portions the tumor elements preponderated, whereas in other places there were relatively few tumor cells scattered throughout the marrow." The cells were of the myeloblastic type, with centrally situated hyperchromatic nuclei and a small amount of rather eosinophilic cytoplasm. The normal structure of the spleen was almost entirely destroyed and the splenic pulp replaced by tumor cells of the type just described. The liver and one periaortic lymph node showed microscopic infiltration by tumor cells.

There has been considerable discussion in the literature regarding the nature of the morbid process in multiple myeloma. Rustizky [16] considered it a hyperplastic process or a benign tumor of marrow cells. Wright [20] drew attention to the fact that in many cases of myeloma the cells are morphologically similar to or identical with the plasma cell of Marschalko. Indeed, the disease was subsequently often called

16. von Rustizky, J.: Deutsche Ztschr. f. Chir. **3**:162, 1873.
17. Arnold, J.: Virchows Arch. f. path. Anat. **57**:297, 1873.
18. Reach, F.: Deutsches Arch. f. klin. Med. **82**:390, 1905.
19. Slavens, J. J.: Am. J. Dis. Child. **47**:821, 1934.
20. Wright, J. H.: J. Boston Soc. M. Sc. **4**:195, 1900.

"plasma cell myeloma." On the basis of this similarity, Maresch [21] went so far as to consider his case one of plasma cell granuloma, i. e., an inflammatory process. However, the cell of myeloma should not be considered as identical with the Marschalko plasma cell. As has been pointed out by Wallgren [22] and Heilmann,[23] it differs in size, staining reactions and other criteria, even in cases that have been called typical instances of plasma cell myeloma.

Many cases have been reported in which the predominant cell was thought to resemble not the plasma cell but the myeloblast.[24] This was true of many elements in our own material. If these cells had predominated, the case might have been called by some an instance of myeloblastic myeloma. However, all transitional forms between these and cells resembling plasma cells were present. This statement is true of other reported instances. Apparently many of the so-called myeloblastic cells are variants, perhaps younger forms, of the typical cell of multiple myeloma. Indeed, Geschickter and Copeland [1] stated that 2 cases considered by one authority to be instances of myeloblastic myeloma were classified by another as cases of the plasma cell type. It was also Wallgren's [22] belief that there was only a slight difference between the two cell types. It seems logical, therefore, to group all the cells under one term, "myeloma cells." [22]

As Klemperer [25] pointed out, the "plasma cell" of the myeloma is not an inflammatory cell. It is an abnormal hematic cell whose origin may be traced to the primitive reticulum cell of the bone marrow, as maintained by Naegeli and by Rohr.[26] Support for this point of view can be derived from the rare cases of myeloma in which the cells have an appearance similar to the more common type but contain hemoglobin (erythroblastic myeloma, Harbitz [27]; see also Magnus-Levy [28]), give a positive peroxidase reaction [29] or even resemble megakaryocytes.[30] Apparently, the myeloma cell may pursue some of its original potentialities of differentiation along myeloid lines.[31]

In classifying as "myeloma cells" all those elements which cannot be definitely identified with any one of the normal bone marrow cells, one reservation must be made, that rarely similar or identical cells may occur in the marrow in other conditions, e. g., agranulocytosis.

If myeloma cells arise from marrow elements, one would expect that they might gain access to the blood stream more readily than cells of

21. Maresch, R.: Verhandl. d. deutsch. path. Gesellsch. **13**:257, 1909.

22. Wallgren, A.: Virchows Arch. f. path. Anat. **232**:381, 1921.

23. Heilmann, P.: Beitr. z. path. Anat. u. z. allg. Path. **80**:652, 1928.

24. Zäh.[3b] Slavens.[19] Wallgren.[22]

25. Klemperer, P.: Beitr. z. path. Anat. u. z. allg. Path. **67**:492, 1920.

26. Rohr, K.: Das menschliche Knochenmark, Leipzig, Georg Thieme, 1940.

27. Harbitz, F.: Norsk mag. f. lægevidensk. **84**:212, 1923.

28. Magnus-Levy, A.: Acta med. Scandinav. **95**:217, 1938.

29. Beck, H. G., and McCleary, S.: J. A. M. A. **72**:480, 1919. Weinberg, F., and Schwartz, E.: Virchows Arch. f. path. Anat. **227**:88, 1920.

30. Gunn, F. D., and Mahle, A. E.: Arch. Path. **26**:377, 1938.

31. Smith, R. P., and Silberberg, M.: Arch. Path. **21**:578, 1936.

other origin. This they actually do. The extreme instances are those in which the condition has been called "plasma cell leukemia."[32] Although resembling leukemia, the condition is very closely related to multiple myeloma, probably representing only a variant of the latter disease. It usually shows a nodular involvement of the marrow by "plasma cells," associated with destruction of bone. In many otherwise typical instances of multiple myeloma the cells may occur in the circulation, particularly preterminally (Gluzinski and Reichenstein, quoted by Ghon and Roman[33]). Piney and Riach[4] even classified cases of multiple myeloma into four groups varying from those of typical myeloma without plasmacythemia to those of plasma cell leukemia with leukemoid visceral and diffuse rather than nodular bony changes.

It becomes apparent, then, that these circulating cells are also not Marschalko plasma cells but myeloma cells. It seems more logical to call such conditions "myeloma cell leukemias" if they are called leukemias at all. Actually, the invasion of the blood stream is not of the proportions or of the character of true leukemia but appears to be an addition to, rather than a replacement of, the normal blood elements.

Despite these dissimilarities, a close relationship apparently does exist between multiple myeloma and myeloid leukemia, based on the origin of these diseases from the same type of cell. One might compare the relationship to that existing between lymphosarcoma and lymphatic leukemia. Both myeloma (or rather myelomatosis) and lymphosarcomatosis can be looked on as systemic diseases of myeloid and lymphatic tissue, respectively. They usually arise in a multicentric fashion, although solitary foci, with subsequent generalization in some cases, undoubtedly occur.[34] In late stages each tends to trespass the limits of its own system, although myeloma in general is less invasive than lymphosarcoma. Finally, the characteristic cells may occur in large numbers in the blood stream.[35]

The question as to the nature of the visceral involvement in multiple myeloma remains. The organs most often involved are the lymph nodes, the spleen and the liver, all tissues previously or potentially the site of myelopoiesis. These organs can be considered as belonging to the hemopoietic system. Are these tissues involved by metastases from the bones or are the myeloma cell foci within them autochthonous (Lubarsch[36])? Both possibilities have been postulated for lymphosarcomatosis[37] and might be expected by analogy to occur in myeloma. In our case the location of foci in the subcapsular sinusoids of the lymph nodes and the nodular character of the infiltration in the liver

32. Piney, A.: Folia haemat. **30**:173, 1924. Muller, G. L., and McNaughton, E.: ibid. **46**:17, 1931. Fleischhacker, H., and Klima, R.: ibid. **56**:5, 1936. Lachnit, V., and Walterkirchen, L.: Wien. klin. Wchnschr. **52**:67, 1939. Lindeboom, G. A., and Mulder, H. J.: Acta med. Scandinav. **108**:363, 1941. Piney and Riach.[4] Osgood and Hunter.[15]

33. Ghon, A., and Roman, B.: Folia haemat. **15**:72, 1913.

34. Bichel, J., and Kirketerp, P.: Acta radiol. **19**:487, 1938.

35. Apitz, K.: Virchows Arch. f. path. Anat. **299**:1, 1937.

36. Lubarsch, O.: Virchows Arch. f. path. Anat. **184**:213, 1906.

37. Ehrlich, J. C., and Gerber, I. E.: Am. J. Cancer **24**:1, 1935.

and the spleen speak for metastases. On the other hand, the exclusive involvement of hemopoietic organs can be interpreted in favor of an autochthonous origin. In the present state of knowledge no decision can be made between the two interpretations.

SUMMARY

A case of multiple myeloma is described in which there was unusually extensive involvement of the spleen and, to a lesser degree, of the liver and the lymph nodes. The renal changes were typical of "myeloma kidney."

The probable origin of myeloma cells from the reticulum of the bone marrow is stressed. It is suggested that the relationship between multiple myeloma and myeloid leukemia may be analogous to that between lymphosarcomatosis and lymphatic leukemia.

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MYOCARDIAL LESIONS IN MYASTHENIA GRAVIS

Review and Report of a Case

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AND JOHN RAO, M.D., DETROIT

In a recent postmortem investigation of a patient with myasthenia gravis, an unusual form of myocarditis was encountered. From a review of all cases in which myasthenia gravis has been examined post mortem since 1901, when its pathologic nature was first established, it is apparent that cardiac involvement has rarely been described in this disease. Because of this we present our case, emphasizing the myocardial lesion rather than the customary thymic tumor and lymphocytic infiltration of skeletal muscles. We thought further that the report would add a new chapter to the subject of myocarditis since in a recent extensive review [1] of the latter condition no mention is made of myasthenia gravis as a disease in which myocarditis may occur. And finally, it was believed important to present our case in view of the negative findings of Taquin and Cooke,[2] who with clinical methods investigated the hearts in 14 cases of myasthenia gravis. Three of the patients subsequently came to necropsy and were found to have normal hearts. No mention is made of the thoroughness with which the organs were investigated histologically.

REPORT OF CASE

A 54 year old white woman was admitted to St. Vincent's Hospital, New York, Nov. 13, 1941, complaining of progressive weakness of two years' duration and intermittent dyspnea which had been present for six days.

The onset was insidious, in October 1939, with blurring of vision, followed soon by dysphagia and dysarthria. In March 1940 she entered a hospital, where a complete study, including a neurologic examination, revealed nothing of note. Thereafter, the weakness continued to progress slowly. Soon she was unable to lift the left eyelid. Later, locomotion grew difficult because of rapid exhaustion of the lower limbs. Finally, the upper extremities were similarly affected. In May 1941, myasthenia gravis was suspected by a physician, who confirmed the diagnosis by demonstrating prompt relief of symptoms with prostigmine therapy. On continuing treatment with the drug, the patient regained strength and weight. She remained well until Nov. 7, 1942, when attacks of dyspnea developed, simulating asthma. The attacks would last for approximately one hour and would recur as often as five times a day. After each episode she was left exhausted to the point of collapse. She was pale and weak and spoke with marked effort. There was slight ptosis of the left lid. A few crepitant and musical rales were heard at the base of the lungs. No enlargement of the heart was made out. The cardiac sounds were poor. There were no murmurs. The rate was 130 and the rhythm regular except for frequent extrasystoles. Abdominal, pelvic and rectal conditions

From St. Vincent's Hospital.

1. Saphir, O.: Arch. Path. **32**:1000, 1941.

2. Taquin, A. C.; Cooke, N. T., and Schwab, R. S.: Am. Heart J. **20**:611, 1940.

were normal. There was pronounced weakness of the extremities. Slight wasting was evident. The neurologic examination yielded nothing pertinent.

Four hours after admission the patient became extremely weak. She could neither talk nor lift her arms. Breathing grew slow and shallow and then stopped, death ensuing.

The outstanding gross finding post mortem consisted of an enlarged thymic mass 7.5 by 5 by 1 cm., weighing 45 Gm. It lay in the normal thymic site over the great vessels. The tumor was roughly oval, encapsulated and freely movable in the surrounding loose areolar tissue. Its outer surface presented a nodular appearance. It was soft and appeared subdivided into smaller nodules by thin fibrous septums. Some of the nodules were solid and red. All were soft. In some the tissue was of pasty consistency, so that it flowed out from the nodules, leaving them as cystic spaces.

The body musculature appeared normal. The heart weighed 330 Gm. Its valves and chambers were unchanged. The myocardium was of good consistency but somewhat pale. The lungs were congested. The trachea and bronchi were normal, as were also the liver, the pancreas and one adrenal. The other adrenal contained a cortical tumor 2 cm. in diameter, diagnosed as adenoma. Each kidney revealed a diffusely, finely granular surface. There was nothing remarkable about the gastrointestinal tract. The brain and the pituitary gland were normal. There was atrophy of the thyroid gland and of the reproductive organs. The spleen was slightly enlarged, weighing 280 Gm. It felt soft and was a pale red. The lymph nodes in the mesentery were prominent, measuring 1 to 2 cm. in diameter. They were solid, discrete and red-gray.

The anatomic diagnosis was: tumor of the thymus; mild atherosclerosis of the aorta; mild congestion and edema of the lungs; splenomegaly; unilateral benign cortical adenoma of the adrenal gland; arteriolonephrosclerosis; atrophy of reproductive organs; enlargement of mesenteric nodes.

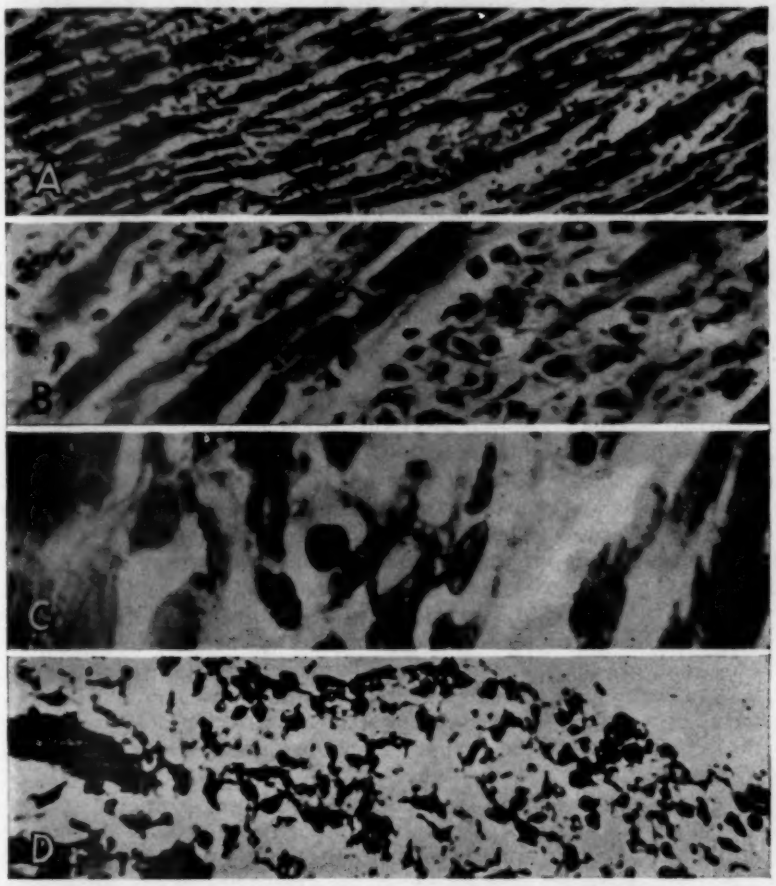
Microscopic Examination.—The capsule of the thymic tumor was thick and fibrous. From it septums ramified throughout the gland, dividing it into small lobules. Within them, the supporting stroma was scant, being limited to the outer surface of blood vessels. These were moderate in number, thin walled and of wide caliber. The lobules contained many cells, more or less compactly arranged. They appeared to be of two types, one a small lymphocyte type and the other a large polyhedral type, the so-called epithelial cell. Those of the latter type were arranged in groups as cords, small sheets and occasionally in an onion peel fashion resembling Hassall's corpuscles. Some lobules presented vacuolation of cells and dissolution. Macrophages were seen filled with hemosiderin, cholesterol crystals and lipoid material. Foreign body giant cells were conspicuous. Just outside the capsule of the tumor one found, surrounded by fat, a number of small flat lobules of normal thymic tissue. They were composed of lymphocytes chiefly, a few epithelial cells and occasional Hassall's corpuscles.

The skeletal muscles (deltoid, pectoral and abdominal) showed small nests of lymphocytes at the periphery of muscle bundles. An occasional muscle fiber was shrunken and its nucleus vacuolated. No bacteria were found.

Since no gross lesions of the myocardium (figure) were in evidence, only four routine blocks through the left ventricle had been saved. All showed extensive diffuse lesions involving the entire thickness of the myocardium and endocardium but not the epicardium. In and among myofibrillae were numerous large irregular cells having scant cytoplasm and oval, round or semilunar-shaped nuclei. None exhibited phagocytosis. Besides these cells one found a few lymphocytes and an occasional polymorphonuclear leukocyte. In addition to cellular infiltration, there

was considerable edema within and between muscle bundles. Occasional small hemorrhages were also seen. Many myofibrils were fragmented and necrotic. It was about these that one found the histiocytes just described. In the endocardium small mounds were seen formed by the same cells observed infiltrating the myocardium. A thrombus covered some of these elevations. No bacteria could be demonstrated.

The coronary vessels and the aorta were normal.



A, photomicrograph of myocardium showing diffuse myocarditis.

B, higher power of one of the cellular areas seen in *A*. Note the separation, thinning and fragmentation of muscle fibers, also the degree and the distribution of the cellular infiltration.

C, photomicrograph showing the cell types in the infiltrate depicted in *B*. The cells are large and spindle-like or stellate in shape.

D, low power photomicrograph showing a focal lesion in the mural endocardium of the left ventricle.

COMMENT

The case described presents a classic clinical example of myasthenia gravis with the usual postmortem findings of thymic tumor and lymphorrhages in skeletal muscle. Unusual, however, was the diffuse myocardial lesion. It appeared to be essentially necrosis of myofibrillae with secondary inflammation, characterized by edema, hemorrhage and infiltration by lymphocytes and large, irregular histiocytes. The lesion could readily be differentiated from the lymphorrhage, on one hand, and from the constituents of the thymic tumor, on the other. The lymphorrhage is a focal, discrete lesion, composed entirely of lymphocytes, present in skeletal muscle, while in the thymic tumor the characteristic element is a large polyhedral epithelial cell with distinct cell outlines. Between the latter cell and the histiocyte observed in the myocardium of our patient, one could see no resemblance. No obvious cause for the myofibrillar necrosis, such as bacterial invasion or coronary disease, was evident on microscopic examination. Cultures were not made.

The question naturally arises as to whether the myocardial lesion is an accidental, nonrelated finding in this case, or whether it forms part of the pathologic picture of myasthenia gravis. An attempt to answer this was undertaken by searching the literature for comparable cases and thus establishing its incidence. Oppenheim [3] had reviewed the literature previous to 1900 case by case. The result of his study was sterile as far as an answer to our question was concerned. Since 1901, when Weigert aroused an appreciation of the pathologic changes in myasthenia gravis, approximately 100 cases with postmortem reports have been recorded. The literature on 92 of these was available to us. It soon became apparent that in a large number of the reports no mention was made of the heart, while in others it was described as grossly normal, but no microscopic evidence was offered as proof of this.

Weigert [4] was the first to note cardiac involvement. It was microscopic in nature. In the myocardium and epicardium in his case he found groups of cells which he regarded as similar to those in the primary thymic tumor. He concluded, therefore, that the lesion represented a metastatic growth. A reconsideration of his case by later students led to the conclusion that the thymic tumor was noncancerous, an opinion to which we adhere.

Four years later, in 1905, Buzzard [5] described in one of his cases "fairly numerous lymphorrhages (groups of lymphocytes) in the myocardium of the left ventricle similar to those found in the skeletal muscle." In a second case he found the capillaries in the myocardium filled with lymphocytes, some of which had escaped from the vessel. Nothing more was written until 1921, when Bouttier and Bertrand [6] noted considerable change in the myocardium in a case of myasthenia gravis. There were edema and dissociation of muscle fibers. In the interstitial tissue were many lymphocytes, mononuclear macrophages

3. Oppenheim, H.: Die myasthenische Paralyse, Berlin, S. Karger, 1901.
4. Weigert, C.: Neurol. Centralbl. **20**:597, 1901.
5. Buzzard, E. F.: Brain **28**:438, 1905.
6. Bouttier, M. H.; Bertrand, I., and Marie, P.: Ann. de méd. **10**:173, 1921.

filled with debris and plasma cells. In 1923 Mella[7] reported the presence of a few lymphocytes in the myocardium.

The last positive observation was made by Barton and Branch.[8] In their case, though the heart appeared grossly normal, microscopic examination disclosed edema of the interstitial tissue and cellular infiltration consisting of many lymphocytes, occasional endothelial cells and rare neutrophils. There was little evidence of muscle degeneration.

That myocardial lesions are reported so infrequently in myasthenia gravis requires explanation. There are two possibilities: (1) that the involvement is really rare and (2) that small focal lesions may be easily missed in random sections such as one of necessity takes from a heart presenting no gross lesions. Which of the two answers is correct, or whether both are correct, must await the recording of careful studies of many hearts. As a preliminary contribution we wish to present a second case of myasthenia gravis on which a postmortem study had been made by one of us (A. R.) in 1936. Fortunately, the entire heart had been preserved, and a more complete study of it was undertaken.

The clinical story was typical of myasthenia gravis. At necropsy a thymic tumor weighing 50 Gm. was found, composed of cords of epithelial cells and lymphocytes. No lymphorrhages were seen in the skeletal muscle. The heart was grossly normal. Many sections were prepared from the ventricles, auricles and valves. All of these, as well as the aorta, proved to be normal. Hence in this one case we can say that a careful study failed to show any cardiac involvement.

A few words must be added to show that we are cognizant of the various forms of myocarditis recently reviewed so well by Saphir and that we attempted to compare the myocarditis in our case with those forms. Thus it became immediately apparent that the myocarditis in this instance was not that described in rheumatic fever, for the lesion was too diffuse and seemed primarily a myofibrillar lesion with a secondary predominantly histiocytic reaction. Infarction was readily ruled out since the blood vessels were normal and the histiologic picture did not resemble an infarct. It is quite possible that the myocardial lesion is an example of isolated myocarditis and as such an accidental finding. The ultimate truth of this must rest on the data added by publication of other cases of myasthenia gravis in which the heart has been carefully studied.

SUMMARY

A case of myasthenia gravis is presented in which diffuse myocarditis and focal mural endocarditis were observed.

The opinion is expressed that the cardiac involvement in this case formed part of the pathologic picture of myasthenia gravis and that it cannot be dismissed simply as a nonrelated finding. A complete review of available literature indicates that cardiac lesions in myasthenia gravis have been described but are rare. Since in most reported cases the hearts were not studied microscopically, it is impossible to be certain of the real incidence of cardiac involvement in cases of myasthenia gravis. In a second instance of myasthenia gravis an extensive study of the heart disclosed only normal conditions.

153 West Eleventh Street.

7. Mella, H. M.: M. Clin. North America **7**:939, 1923.
8. Barton, F. E., and Branch, C. F.: J. A. M. A. **109**:2044, 1937.

General Reviews

EFFECTS OF RADIATION ON NORMAL TISSUES

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III. EFFECTS OF RADIATION ON THE BLOOD AND THE HEMOPOIETIC TISSUES, INCLUDING THE SPLEEN, THE THYMUS AND THE LYMPH NODES

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The effect of roentgen rays and radioactive substances on the circulating blood has been studied sporadically since 1903. In that year Heineke first described the damage suffered by the hemopoietic organs of animals and Senn discovered the beneficial effects of roentgen rays in human leukemia. Subsequent interest in the therapy of leukemia has somewhat overshadowed the importance of radiation changes in the blood of persons with no primary blood disorder.

In spite of the hazard of blood damage as an undesirable side effect of radiation therapy, few concise data are accessible on the changes in the blood to be expected even from standardized radiologic procedures. Therefore, it seems timely to assemble what information is available in the hope that it may be useful to radiologists in protecting themselves and their patients, that it may help pathologists in interpreting radiation changes and that it may stimulate experimental interest in a fascinating field where exact information is so badly needed.

In practical radiation therapy, serious damage of the blood seldom results from local treatment of tumors. The dangers, however, are increasing as radiologic advances introduce larger and larger total doses. With some technics, such as the internal administration of radioactive isotopes and irradiation of the entire body, the limiting factor in dosage has already shifted from "cutaneous tolerance" to "hemopoietic tolerance."

As a practical generalization it may be said that sufficient irradiation of tissues with either radium or roentgen rays will cause reduction in the numbers of cells of all series in the circulating blood and will produce variable changes in the plasma constituents.

When biologic material is irradiated, some alterations in the tissues may be seen almost immediately (Heeren, 1936), but most of the changes appear only after a significant latent period (Packard, 1931). Thus, lymphopenia may be found within a few minutes after heavy

irradiation, granulopenia develops hours later, while erythropenia is rarely seen until several days or weeks have elapsed. These changes, once established, may be progressive for weeks or months without further irradiation of tissues. Since the primary injury is inflicted during the actual period of exposure, the blood abnormalities appearing subsequently are best considered as secondary effects.

Any deviation from normal in the circulating cells or the plasma is immediately opposed by the blood-regulating mechanisms. These mechanisms, operating to restore every blood constituent to its proper level, often overcompensate for and reverse initial changes. Normal physiology supplies many examples of such behavior. For instance, ingestion of dextrose produces transient hyperglycemia. Sugar metabolism is accelerated and the venous blood sugar then falls to hypoglycemic levels. Many constituents of the blood respond to radiation in a similar biphasic manner. Thus, after ordinary therapeutic doses of radiation, the number of neutrophils in circulation characteristically rises above normal and then falls abruptly below normal. The lymphocytes respond in similar fashion to very small doses, and in a few cases the same type of fluctuation has been produced in the red cell count by repeated small doses.

Sometimes it has been possible to produce prolonged lymphocytosis [1] or erythrocytosis [2] by single, repeated or chronic exposure to, very small doses. Some writers have seen in this phenomenon an expression of the Arndt-Schulz law, namely, that small doses are stimulating and large doses destructive. Isaacs went further and claimed that all doses are stimulating to the blood cells. He expressed the belief that young cells in the hemopoietic organs are stimulated to division and maturation, while the process of maturation, senility and death is hastened in adult circulating cells. Packard (1931), Czepa, Holzknecht (1923), Rolleston, Pordes (1923) and Desjardins (1932a) did not accept this view. They maintained that direct stimulation of cells by radium or roentgen rays has never been demonstrated and that the observed biologic responses are best explained as reactions to injury.

The most important single factor determining the degree of the blood changes and the rate at which they develop is the dose of radiation absorbed by the subject. Any statement of dosage should include as a bare minimum the number of roentgens delivered and the size of the field exposed. Failure to record the size of the field has rendered much laborious work quantitatively meaningless. It is as though a meteorologist should report that one-half inch (1.27 cm.) of rain had fallen within the watershed of a reservoir without stating whether it fell over 1 square mile or 100 square miles (2.5 or 250 square kilometers). Doses that can be adequately calculated from the data given

1. Murphy. Nakahara and Murphy. Russ and others (1919).
2. da Silva-Mello. Westman. Zadek.

show a fairly good correlation with the resulting blood changes (Goodfellow; Minot and Spurling). The greater the dose the more profound is the blood damage, the more rapidly it develops and the more slowly it is repaired (Goodfellow). The blood response remains quite consistent qualitatively over a wide range of dosages, although massive exposures may obscure some of the early changes and small doses sometimes fail to evoke the complete response.

A number of other technical factors besides dosage affect the result. The influence of different wavelengths of radiation on biologic responses is still under dispute, and the question must remain open until more accurate dose measurements and biologic indicators are available. When proper corrections for absorption are made, there is no convincing evidence at hand of qualitative or quantitative differences in the biologic effect of similar doses delivered at wavelengths within the range of soft and hard roentgen rays, gamma rays and alpha and beta particles of radium.[3]

The minute intensity of radiation is probably of more importance than the wavelength (Langendorf; Pack and Quimby). Holthusen (1933) presented graphs indicating that 500 r delivered in one minute produces the same biologic effect as 900 r given in fifty minutes or 1,400 r given in eight hours. As the intensity is further reduced, the biologic effect of ordinary doses becomes negligible until, at a rate somewhere in the neighborhood of 0.0005 r per minute, no effect can be expected with any dose.

A result comparable to that obtained with low minute intensities is achieved by delivering fractional treatments separated by rest periods. Under these conditions there is incomplete summation of the divided doses (Liechti, 1929), and less blood damage results than if the total dose had been given at a single sitting (Gloor and Zuppinger). It is sometimes stated that fractionated treatments produce greater damage of the blood than large single treatments (Mouquin). This is true only so far as larger total doses may be administered by the fractional method than could be tolerated in a single treatment.

Certain biologic considerations are of equal importance with the technical factors just mentioned. Marked species variations in radiosensitivity have been noted by several authors. Rats and guinea pigs are said to be more radiosensitive than dogs, cats or rabbits, while reptiles, amphibia and birds can tolerate several times the lethal dose for mammals (Hartoch and Israelski; Warren and Whipple). Man is probably among the more radiosensitive of the mammals. The general character of the blood changes is very similar from species to species (Taylor, Witherbee and Murphy), and every type of radiation change found in human blood has been experimentally reproduced in laboratory animals.

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3. Packard (1936). Liechti (1929). Holthusen (1933). Goodfellow.

Even within an apparently homogeneous group of the same species there are individual variations in radiosensitivity amounting to as much as 20 to 50 per cent.[4] Differences in age or health increase these variations. Young subjects[5] and patients who are anemic, leukopenic, infected or debilitated (Heim; Stetson) are more susceptible to injury of the blood by radiation than normal adults.

The same dose of radiation gives a different degree of blood damage depending on what part of the body is exposed. Irradiation of the abdomen is found to produce greater changes in the blood than treatment over the chest, head or extremities.[6] These regional differences in the effectiveness of radiation are greater than can be explained by any differences in the amount of blood or of hemopoietic tissue included in the various fields of treatment.

Considerations of this sort raise the interesting problem of the mechanisms through which radiation alters the peripheral blood picture. It would be of practical clinical value to know whether the cytopenias are produced by destruction of circulating cells, direct damage of the hemopoietic tissue or some diffuse injury to the blood and blood-forming organs.

In an attempt to study the radiosensitivity of blood cells uncomplicated by somatic reactions, a number of observers have irradiated blood in vitro. The results reveal surprising radioresistance of the cells.[7] Enormous doses, often ranging above 20,000 r, may be administered before hemolysis of red cells[8] and destruction of leukocytes[9] take place. Similar radioresistance is shown by blood cells retained in an extremity by a tourniquet or incarcerated within a blood vessel by ligation at two points (Baermann and Linser; Spurling and Lawrence).

Bone marrow and fixed lymphoid tissue are found to be somewhat more radiosensitive in vitro than free blood cells but survive large doses.[10] In vitro observations have failed, therefore, to reveal whether blood damage in vivo results chiefly from destruction of circulating cells or from injury to blood-forming organs.

Studies on blood responses to radiation in human beings and laboratory animals lack the nicety of those based on in vitro methods but do

4. Cornil and Rouslacroix. Duffy and others. Lambin. Minot and Spurling. Strauss.

5. Lacassagne, Lavedan and de Léobardy. Woenckhaus (1936).

6. Dodds and Webster. Hayer. Heim. Woenckhaus (1928). Zumpe.

7. Baermann and Linser. Bergonié and Tribondeau. Knott and Watt. Milchner and Mosse. Russ and others. Spurling and Lawrence.

8. Holthusen (1922-1923). Levin and Piffault. Redfield and Bright. Rogozinski and Levin. Salomonsen and Dreyer. Woodard.

9. Doljanski and Halberstaedter. Lacassagne and Gricouroff. Neumann. Russ and others.

10. Gregori. Jansson. Meldolesi and Giusti. Stenstrom and King.

suggest in part the mode of action of absorbed radiation. Heavily treated subjects show excess phagocytosis of red cells in the lymphoid organs [11] and large deposits of hemosiderin in the spleen, lymph nodes, bone marrow and liver.[12] This suggests some degree of destruction of circulating red cells. Massive exposures produce severe leukopenia within a few hours (Mayneord and Piney), and such a rapid drop suggests destruction of leukocytes in circulation. A more striking and consistent finding in heavily irradiated animals is the widespread cell destruction in the blood-forming organs.[13] This type of injury is probably of far greater consequence in determining the peripheral blood picture than any destruction of cells already in circulation.

Typical and even fatal damage of the blood may result, however, from heavy or repeated irradiation of a part of the body which contains only a small proportion of the total hemopoietic tissue.[14] Histologic study of subjects treated in this fashion shows massive destruction of any hemopoietic tissue within the field of treatment and lesser degrees of damage to bone marrow and lymphoid organs throughout the body. The blood reflects massive radiation damage to any tissue whether or not that tissue is directly concerned with blood formation. Rapid destruction of large radiosensitive tumors will produce blood changes indistinguishable from those which follow direct irradiation of the bone marrow. It is not known how local irradiation affects distant tissues. A common, but unproved, assumption is that tissues damaged within the field of treatment release toxic breakdown products which are taken into general circulation and thus injure distant tissues.

In spite of the lack of final evidence, it is probable that most of the changes in the blood picture after irradiation of tissues are due to a combination of direct and indirect damage to the blood-forming organs, while destruction of circulating cells plays only a minor role.

Since Heineke's pioneer work in 1903 and 1904, over a thousand articles have been published on blood changes induced by radiation. Brief abstracts of more than a hundred and fifty of them may be found in a review published by Selling and Osgood. The average quality of these reports is somewhat below the general standard of medical literature, due in part to the intrinsic difficulties of the problem. There are relatively few investigators well enough trained in biology, hematology and radiation physics to avoid all the pitfalls inherent in these three fields. The most common shortcoming of the published work is inadequate

11. Clarkson and others. Ross. Thomas and Bruner. Tsuzuki.

12. Clarkson and others. den Hoed and others. Piney. Ssipowsky. Thomas and Bruner. Tsuzuki. Wegelin.

13. Heineke (1904). Lacassagne and Lavedan. Siciliano and Banci-Buonamici. Ssipowsky. Tsuzuki.

14. Aubertin and Beaujard (1905). Benjamin, von Reuss and others. Siciliano and Banci-Buonamici. Ssipowsky. Zumpe.

statement or interpretation of radiation doses. A standard unit of physical dosage has been in use for only fourteen years (international roentgen, 1928), and no biologic unit has been invented which attempts to include the variables noted in the foregoing pages. In comparing two pieces of work, the biologic doses may be estimated as large, moderate or small, but finer distinctions are not significant unless the conditions of the irradiation are very completely described.

A second source of confusion has been the progressive nature of the blood changes. Observations taken six hours after treatment may be in apparent conflict with the findings six days later. The complete picture of the response of any blood constituent to radiation is revealed only by repeated determinations at short intervals throughout the course of the reaction—a procedure so laborious to the investigator and so unpleasant to the subject that it has seldom been used.

Any review of this body of literature which attempted to present both sides of all controversial questions would suffer in clarity and usefulness. A somewhat arbitrary selection of material has therefore been made in an attempt to stress what appear to be the more plausible conclusions.

BLOOD CELLS

Lymphocytes.—Lymphocytes are generally regarded as the most radiosensitive cells in the body.[15] A drop in the lymphocyte count is the earliest, most marked and most consistent blood change induced by therapeutic radiation (Minot and Spurling).

The minimum dose necessary to depress the level of human lymphocytes has not been determined, but it is certainly small. In rabbits a dose of 22 r is said to be effective (Mayneord and Piney), and rats are said to show a response to very much smaller doses (Russ). The claim that the circulating lymphocytes of rats may be "even more delicate indicators to x-rays than is an ordinary x-ray plate" (Russ, Chambers and Scott) still awaits confirmation.

Lymphocytes show not only high radiosensitivity but also a remarkable ability to recover from severe radiation damage. Both these characteristics may well be related to the short natural life expectancy of lymphocytes, their rapid replacement in the circulation and the associated regenerative activity of lymphopoietic tissue.

Minot and Spurling in 1924 published one of the most adequate clinical studies available on the blood changes after therapeutic irradiation of nonleukemic patients. They found a prompt decrease in the number of circulating lymphocytes in practically every case after intensive short wave therapy. The fall was greatest during the first twenty-four hours but continued downward for three to five days. The lymphocyte count

15. Desjardins (1932 *a*). Goodfellow. Heineke (1904). Mayneord and Piney. Minot and Spurling. Taylor, Witherbee and Murphy.

remained near this minimum level for several more days before a gradual recovery set in, reaching normal only after a period of three to five weeks. The mean absolute depression of the lymphocytes was almost 1,000 cells per cubic millimeter, which amounted to 50 per cent of the mean preirradiation count. The relative lymphopenia was quite variable because of fluctuations in the granulocyte count but in extreme cases reached a low point of 1 to 3 per cent of the total white cell count. The degree and the duration of the lymphopenia showed fairly good correlation with the dose of radiation and with the size of the field exposed. Heavier doses to larger fields produced a more abrupt fall to lower levels and a slower recovery. These results are in general agreement with earlier work and have been repeatedly confirmed.[16]

The recovery phase is remarkable in that it so often overshoots the mark and gives rise to absolute or relative lymphocytosis of long duration. This result has been observed in patients [17] but is more common among radiologists who are chronically exposed to small doses of radiation.[18] In laboratory animals, protracted lymphocytosis, preceded by ephemeral lymphopenia, may be produced at will by exposures to very minute doses.[19] The initial lymphopenia suggests that the subsequent lymphocytosis is not the result of direct stimulation but a reaction to injury.

The recovery of lymphocytes from injury is extremely rapid and effective. Recognition of this fact is somewhat obscured by reports in the literature that after single large doses of radiation the number of lymphocytes returns to the preirradiation level somewhat more slowly than the number of neutrophilic polymorphonuclear leukocytes.[20] However, the lymphocytes, being more radiosensitive, suffer a greater reduction in number and are called on to recover from much lower levels. In returning to normal almost as rapidly as the neutrophils they accomplish a far greater percental recovery. After repeated small doses the number of lymphocytes rebounds quickly from each slight injury,[21] while the neutrophils show a less adequate response. The usual result is mild leukopenia with relative lymphocytosis, such as may often be found in persons subjected to occupational exposure to radiation.

Neutrophilic Polymorphonuclear Leukocytes.—Neutrophilic polymorphonuclear leukocytes are somewhat less radiosensitive than lymphocytes but recover less adequately after injury. The characteristic

16. Bosch. Goodfellow. Kornblum and others. Mayneord and Piney. Westman (1925).

17. Bosch. den Hoed, Levie and Straub.

18. Amundsen. Cornil and Rouslacroix. Gudzent and Halberstaedter. Ordway. Pfahler. Piney. Portis.

19. Nakahara and Murphy. Murphy. Russ, Chambers, Scott and Mottram.

20. Minot and Spurling. Taylor, Witherbee and Murphy.

21. Amundsen. Kornblum and others. Russ, Chambers, Scott and Mottram.

response in man and animals to fairly heavy therapeutic doses of radiation is very brief leukopenia (Lavedan, 1932) followed by leukocytosis. The total white cell count may rise as much as 50 per cent above normal, the increase being made up almost entirely of neutrophils.[22] The leukocytosis begins about two hours after treatment, reaches a maximum in some twelve hours and falls sharply to normal or below in twenty-four to seventy-two hours (Minot and Spurling). Neutropenia of variable degree then supervenes, reaching a minimum level six to eight days after treatment, with recovery to normal in three to eight weeks (Kornblum and co-workers; Minot and Spurling). Repeated treatments are followed each by a tide of leukocytosis diminishing in degree with each successive exposure.[23] If the treatment is repeated before recovery is complete, the early leukocytosis is less and the subsequent neutropenia is greater and lasts longer (Minot and Spurling). Some workers have failed to note the brief early leukocytosis because blood counts were not made within a few hours after treatment, but it is probably a constant response to both small and large doses.[24] Small doses produce mild neutrophilia lasting in some cases as long as ten days,[25] but radiation neutrophilia of longer duration is a rare finding.[26] When larger doses are given, the leukocytic phase is shorter, neutropenia appears earlier and is more profound, and recovery is delayed (Minot and Spurling). In extreme cases, recovery fails, and progressive neutropenia may go on to agranulocytosis and death.[27]

After heavy irradiation of tissues degenerated neutrophils appear in circulation,[28] but there is little agreement as to how numerous they are, how soon they appear and disappear and whether they represent mature cells damaged in circulation or the product of damaged bone marrow. The more severe the leukopenia, the more plentiful the damaged cells become. Minot and Spurling found that these cells might make up 20 to 30 per cent of the total white cell count during the first three days after treatment and were still present in smaller numbers two to three weeks later.

Evidences of bone marrow activity appear very shortly after radiation treatment. The earliest indication is an increase in the percentage of young neutrophils in circulation, a change usually expressed as a "shift

22. Arnold. Aubertin and Beaujard (1905). Desjardins and Marquis. Kornblum and others. Minot and Spurling. Mayneord and Piney. Westman (1925).

23. Arnold. Goodfellow. Lavedan (1932).

24. Gloor and Zuppinger. Lacassagne and Lavedan. Zacherl.

25. Gloor and Zuppinger. Hayer. Minot and Spurling.

26. Aubertin (1931 *c*). Maingot and others.

27. Goudsmit and Levie. Hamperl. den Hoed and others. Levitt. Marchal and others.

28. Aubertin and Beaujard (1905, 1908). Goodfellow. Minot and Spurling.

to the left" in the Schilling or the Arneth count.[29] Mayneord and Piney reported an increase in rabbits of class I neutrophils (the youngest class) from 28 per cent before irradiation to 80 per cent seventeen hours later. This change, together with a sevenfold increase in the total number of neutrophils, indicates an enormous addition of young cells from the marrow.

In rabbits an increase in young cells has been observed within an hour after treatment (Kennedy and Grover), but in human beings it is usually seen for the first time several days later (Minot and Spurling). Young cells persist in circulation until the neutrophil count has returned approximately to the preirradiation level (Minot and Spurling). Truly immature cells, such as myelocytes and myeloblasts, appear in circulation only rarely.[30] The presence of more than 2 or 3 per cent of these cells should raise the question of serious damage of the bone marrow, even in the absence of marked leukopenia.

The recovery of the neutrophils from irradiation is somewhat less adequate than that of the lymphocytes but is almost always sufficient to correct the minor changes induced by routine therapy. Some radiologists who use large doses set an arbitrary level, such as 3,000 leukocytes per cubic millimeter, below which they do not care to depress a patient's white cell count (den Hoed and co-workers; Levitt). However, recovery has taken place from radiation leukopenia of less than 500 white cells per cubic millimeter (den Hoed and co-workers; Levitt). It is probable that severe neutropenia produced acutely by a single massive exposure carries a better prognosis than the same degree of neutropenia produced gradually by repeated exposures (Mayneord and Piney). Thus a white cell count of 2,000 for a radiologic worker would indicate a more serious condition than the same count for a patient a few days after therapeutic exposure.

Radiation neutropenia is very refractory to all kinds of treatment. Injections of pentnucleotide (Hamperl; Kimm and Spies), liver extract and typhoid vaccine (Kornblum and co-workers) fail to elicit the normal leukocytic response, and blood transfusions produce only brief improvement (Larkins). Reports of good results following administration of vitamin B (Weicker and Bublitz) and vitamin C (Carrié) await confirmation. The present treatment consists in general supportive measures and complete protection from further irradiation.

Eosinophils, Basophils and Monocytes.—The reactions of eosinophils, basophils and monocytes to irradiation have not been thoroughly worked

29. Aubertin and Beaujard (1908). Gallavresi. Bock. Feller and Langer. Gloor and Zuppinger. Goodfellow. Hayer. Kennedy and Grover. Mayneord and Piney. Minot and Spurling. Zumpe.

30. Arnold. Aubertin and Beaujard (1905). Bock. Cornil and Rouslacroix. Goodfellow. Gallavresi. den Hoed and others. Portis. Thomas and Bruner.

out. Significant changes are occasionally seen in the number of these cells, but they are not regular or predictable.

After therapeutic irradiation the number of eosinophils sometimes decreases slightly for a few days but generally returns to the preirradiation level two to three weeks later. At this time a few patients show definite eosinophilia amounting to as much as 10 to 20 per cent of the total white cell count.[31] A similar eosinophilia is seen occasionally in radiologists[32] and has been experimentally produced in laboratory animals.[33]

The behavior of the monocytes can be described in almost the same words. Ordinarily no significant change is seen after irradiation, but monocytosis has developed in a few patients[34] and radiologists (Aubertin, 1912; Piney) and a few experimental animals.[35] Significant changes in the number of circulating basophils have seldom been reported (Weitz).

Platelets.—The evidence on the behavior of blood platelets after irradiation of tissues is also fragmentary. Minot and Spurling found a mild increase in platelets during the first three days after moderate doses. Heavier doses resulted in an immediate slight rise followed by a fall below normal and recovery to normal or above within a week. A considerable rise in platelets has been noted after small or moderate doses,[36] although some authors find no significant changes. It is certain, however, that heavy radiation to large fields can produce an early and profound drop in the platelet count,[37] sometimes associated with purpura, hemorrhage and death.[38]

Erythrocytes.—The circulating red cells are less easily affected by radiation than are the leukocytes, owing to greater radioresistance of the cells themselves and also to the ability of erythropoietic foci in the bone marrow to withstand doses of radiation that are destructive to leukopoietic tissue.[39] The high tolerance of the red cell does not seem to depend on its lack of a nucleus, since the nucleated cells of birds are equally resistant (Warren and Whipple).

31. Minot and Spurling. Bock. Goodfellow. Sabrazès.

32. Aubertin (1912, 1932). Cornil and Rouslacroix. Pfahler. Piney. Weitz.

33. Aubertin and Beaujard (1908). Petersen and Soelhof.

34. Goodfellow. Lavedan (1932). Mayneord and Piney. Minot and Spurling.

35. Mayneord and Piney. Piney. Lambin (1931).

36. Bucky and Guggenheimer. Falconer and others. Mottram (1923 *d*). Duke.

37. Mottram (1923 *d*). Ducuing and others. den Hoed and others. Fabricius-Möller. Helber and Linser. Lacassagne and others (1922). Shouse and others. Duke. Craver and MacComb. Martland (1929). Cramer and others.

38. den Hoed and others. Marchal and others. Lacassagne and others (1922). Ducuing and others. Shouse and others.

39. den Hoed and others. Milchner and Mosse. Aubertin and Beaujard (1905). Vallebona and Capocaccia. Heineke (1905). Tsuzuki.

Sufficiently large doses of radiation result in changes in the permeability of the red cell membrane. Ting and Zirkle found that after exposure of human or beef erythrocytes to 33,000 r the cell membranes became permeable to sodium and potassium ions while remaining impermeable to magnesium ions. As a result, the cell volume increased as demonstrated by the hematocrit, and hemolysis set in fifteen or twenty hours after irradiation. A similar increase in permeability to chloride ion has been described by Lehmann and Wels, and several workers have noted increased susceptibility to hemolysis in irradiated cells.[40] After therapeutic doses of radiation an increase in the average red cell volume has been described (Koch), although some authors have found no such change (De Niord and co-workers). The increased phagocytosis of red cells in the spleen and lymph nodes of heavily irradiated animals (Clarkson and co-workers; Tsuzuki) also suggests some sort of change in the red cells, since the reticuloendothelial phagocytes show no increased avidity for bacteria or neutral dyes after such treatment.[41]

Moderate irradiation seldom results in a significant fall in the red cell count or the hemoglobin. However, degenerating red cells appear in circulation, the reticulocyte count is increased, iron pigment accumulates in the reticuloendothelial cells, and in rare cases the serum bilirubin is slightly elevated.[42] These findings, taken together, suggest a compensated destruction of circulating red cells. If sufficient radiation is given, the bone marrow is irreparably damaged, compensation fails and anemia appears.

Radiation anemia is generally described as "aplastic" [43] and is of all grades of severity, ranging from a borderline condition to those with red cell counts of less than 1,000,000. Wegelin and Martland expressed the belief that true "aplastic" anemia with aplasia of the bone marrow results from external application of radiation, while "regenerative" anemia with hyperplastic marrow is produced by radioactive salts deposited in the body. The work of other investigators does not support any sharp differentiation between the types of anemia produced by radiation applied externally and that applied internally. The hyperplastic marrow, described so well by Martland in human cases of radium and mesothorium poisoning, has also been seen in human beings and animals subjected only to external roentgen radiation.[44]

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40. Woodard (1938). Pearse. Salomonsen and Dreyer.

41. Teneff and Stoppani. Schwienhorst. Schönig.

42. Kaznelson and St. Lorant. Wright and Bulman. den Hoed and others.

43. Pfahler. Wegelin. Haagensen. Piney. Brinnitzer. Faber. Jaulin. Larkins. Mottram (1920 *a*).

44. Gendreau and Pinsonneault. Aubertin and Beaujard (1905 and 1908). Piney. Pappenheim.

Radiation anemia shows no peculiarities of blood picture which mark it off definitely from other types of anemia, although it does differ from most forms of secondary anemia in that the color index is frequently above 1.[45]

It is quite common, particularly in cases of the milder grades, to find the red cell count and the hemoglobin proportionately reduced with little apparent abnormality in the color, size or shape of the red cells (Larkins). A considerable number of cases, on the other hand, show anisocytosis and poikilocytosis, often of marked degree,[46] hypochromia,[47] polychromasia,[48] and sometimes macrocytes and megalocytes.[49] Reticulocytes are increased in number during the early phase of the reaction and sometimes during the recovery phase [50] but often disappear from circulation while anemia is developing (Ducuing and co-workers). Circulating normoblasts are generally found only in small numbers if at all.[51] The icteric index usually remains within normal limits,[52] but may be slightly elevated.[53] This picture, coupled with leukopenia and relative lymphocytosis, is sometimes difficult to distinguish from pernicious anemia.[54]

Several observers have noted that irradiation produces a wave of red cell regeneration, evidenced by an increased reticulocyte count.[55] In a few human beings a prolonged increase in the hemoglobin and the red cell count has followed irradiation. Patients undergoing therapeutic irradiation only rarely show definite erythrocytosis (Westmann, 1921-1922), and most of the examples of this effect on the blood are found among roentgenologists.[56] The evidence at hand suggests that radiation erythrocytosis is often accompanied by a color index below 1, while in radiation anemia the color index is more often elevated (Cornil and Rouslacroix).

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45. Feller and Langer. Moldawsky. Mottram (1920 *a*). Clarkson and others. Cornil and Rouslacroix. Martland (1926 and 1929).

46. Feller and Langer. Aubertin and Beaujard (1905). Clarkson and others. Martland (1926). Thomas and Bruner. Reitter and Martland.

47. Cornil and Rouslacroix. Reitter and Martland. Wegelin.

48. Clarkson and others. Thomas and Bruner. Martland (1926). Aubertin and Beaujard (1905).

49. Wegelin. Bock. Martland (1926).

50. Gallavresi. Lambin (1931). Mardersteig (1937 and 1938 *b* and *c*). Langendorf. Reisner. Rosenthal and Grace.

51. den Hoed and others. Gendreau and Pinsonneault. Wegelin. Rosenthal and Grace. Reitter and Martland. Lambin (1931). Clarkson and others. Martland (1926).

52. Craver and MacComb. Lambin (1930). Martland (1926 and 1931). Graham.

53. Wright and Bulman. Kaznelson and St. Lorant. den Hoed and others.

54. Martland (1926 and 1929). Wegelin.

55. Moldawsky. Reisner. Mardersteig (1937 and 1938 *b*). Lambin (1931). Langendorf. Gallavresi. Gérard.

56. Cornil and Rouslacroix. Piney. Mottram (1921 *c*). Moldawsky. Pfahler.

In practice it is difficult to predict how the red cells of any single person will respond to a fixed technic of irradiation, but certain generalizations can be drawn concerning the results of the three main types of exposure, namely, radiation therapy, occupational exposure and experimental exposure of animals.

Patients undergoing therapy, even by the protracted or fractionated methods, are subjected to a relatively acute injury. No abrupt change in the red cells is to be expected after a single therapeutic exposure, and most patients tolerate a course of therapy without material change in the red cell count or the hemoglobin.[57] In the second or third week after beginning a series of treatments, some patients show a slight to moderate drop in both the red cell count and the hemoglobin, with recovery to normal in two to three months.[58] Serious anemia occasionally results from radiation therapy, usually in previously anemic or debilitated persons who receive long-continued or massive roentgen therapy or in patients subjected to internal administration of radioactive material.[59] It must be kept in mind that the blood picture of the patient is frequently complicated by changes due to the disease for which he is being treated. Adequate radiation therapy may even relieve the cause of preexisting anemia in such conditions as bleeding carcinoma of the cervix, functional uterine bleeding or leukemia. In these conditions the red cell count often improves following treatment (Forkner; Lavedan, 1932). Anemia alone is seldom a contraindication to radiation therapy (Forkner; Piney), although care should be exercised in retreating patients who have already suffered considerable damage to the marrow.

Occupational exposure to roentgen rays and radium involves repeated absorption of small doses over a long period. It appears that erythropoietic tissue, although more resistant than leukopoietic tissue to damage by radiation,[60] shows poorer powers of recovery once it has been injured. Repeated slight insult may thus bring about irreparable damage to erythropoiesis without completely overwhelming the powers of recovery of leukopoietic foci. Occupational exposure satisfies these conditions admirably, and the blood of poorly protected radiologic workers characteristically shows leukopenia with relative lymphocytosis, coupled with various grades of anemia.[61] Some persons with roentgen ray anemia

57. Kornblum and others. Desjardins and Marquis. Richman. Gloor and Zuppinger. Minot and Spurling. Bosch. Case. Westman (1925).

58. Richman. Bosch. Case. Bock. Lavedan (1932). Gallavresi.

59. Gettler and Norris. Lambin (1930). Aub and others. Goudsmit and Levie.

60. den Hoed and others. Milchner and Mosse. Aubertin and Beaujard (1905). Vallebona and Capocaccia. Tsuzuki.

61. Reitter and Martland. Mottram (1920 *a*). Feller and Langer. Wegelin. Piney.

die,[62] but the majority slowly recover if protected from further exposure. Anemia in persons who work with radioactive substances may be due to external exposure to radiation but often results from deposition of radioactive salts in the body. In the latter case it carries a poorer prognosis than roentgen ray anemia, since it is impossible to remove the patient from continued exposure.[63]

The development of radiation anemia in a radiologic worker indicates grossly inadequate protection. Slight overexposure should not depress the red cell count even though the leukocytes may show radiation changes.[64] The occasional examples of erythrocytosis in radiologists have already been noted. In all the cases reported so far, the condition has been asymptomatic. It should be mentioned further that Moldawsky, in examining the blood of over 35 radiologic workers, found reticulocytosis in every one of them, sometimes amounting to over 20 per cent of the red cells, and Gérard expressed the belief that reticulocytosis is the commonest modification seen in the blood of radiologists.

Experimental irradiation of animals has served to confirm and expand the information obtained from observing human beings. A reduction in the number of red cells in the circulating blood can be obtained with very heavy single doses but occurs later than the changes in the lymphocytes and polymorphonuclear leukocytes.[65] Acute anemia usually precedes death from lethal irradiation, but after sublethal exposure anemia develops more slowly and is followed by slow recovery (Wright and Bulman). Irradiation of the total body is much more effective in reducing the red cell count and the hemoglobin than that of smaller fields (Clarkson and co-workers; Ducuing and co-workers). Small fractionated treatments produce anemia with minimum damage to the general health of the animal (Benda and co-workers; Lacassagne and Lavedan). Injected, ingested or inhaled radioactive material affects the red cell count in a manner similar to radiation [66] externally applied.

Occasionally polycythemia is seen in experimental animals following small or repeated doses of external or internal radiation.[67] In the same animals anemia may subsequently develop without further treatment (Krömeke).

The blood picture of radiation anemia in laboratory animals resembles that seen in human beings. Some animals show nothing beyond a simple

62. Gendreau and Pinsonneault. Larkins. Faber. Mottram (1920 *a*). Jaulin. Gavazzeni and Minelli. Lambin (1930). Wegelin.

63. Martland (1926 and 1929). Mottram (1920 *a*). Lambin (1930). Reitter and Martland. Gendreau and Pinsonneault.

64. Pfahler. Kaplan and Rubenfeld. Gudzent and Halberstaedter. Mottram (1921 *c*). Portis. Ordway. Reid.

65. Gregori. Wright and Bulman. Clarkson and others.

66. Lambin (1931). Thomas and Bruner. da Silva-Mello. Zadek. Cluzet and Chevallier. Rosenthal and Grace.

67. da Silva-Mello. Zadek. Cluzet and Chevallier.

reduction of the number of red cells and of hemoglobin, while others show a high color index,[68] anisocytosis,[69] poikilocytosis,[70] polychromasia [71] and nucleated red cells.[72] Reticulocytosis has been observed soon after exposure and also during recovery from radiation anemia.[73] In experimental animals, as in human beings, the anemia does not ordinarily appear until a week or more after treatment [74] but then may become progressively severe without further exposure.[75] Severe anemia is produced more rapidly and with smaller doses of radiation in very young animals than in adults.[76]

"Radiation Leukemia."—Insufficient study has been devoted to the regeneration of the blood and the hemopoietic tissue after damage by radiation. However, it is known that shortly after exposure, while the blood counts are still falling, immature cells of all series begin to appear in circulation.[77] As the blood counts are restored to normal, these evidences of regeneration gradually disappear from the circulating blood. Occasionally the regenerative process overshoots the mark, giving rise to benign lymphocytosis. Less commonly erythrocytosis, neutrophilia, eosinophilia or monocytosis is found. The circulating blood does not accurately reflect the state of activity of the hemopoietic organs. Lymph nodes and bone marrow may be found in a hypoplastic or a hyperplastic state long after the blood picture has returned to normal. Martland (1931) in a study of occupational radium and mesothorium poisoning found that the blood picture in many of his cases was within normal limits, while the bone marrow showed such marked degrees of hyperplasia and immaturity that "it would seem very likely that a myeloid leukemia could easily develop."

Actually, few examples of leukemia have been described in persons chronically exposed to radiation. Only 24 case reports are found in the literature [78] if one excludes all reports of leukemia following therapeutic

68. Clarkson and others. Benda and others.

69. Rosenthal and Grace.

70. Aubertin and Beaujard (1905). Rosenthal and Grace. Clarkson and others.

71. Aubertin and Beaujard (1905). Clarkson and others.

72. Aubertin and Beaujard (1905). Clarkson and others. Rosenthal and Grace. Lambin (1931). Linser and Helber.

73. Mardersteig (1938 *b*). Langendorf. Reisner.

74. Wright and Bulman. Aubertin and Delamarre. Benda and others.

75. Krömeke. Benda and others.

76. Woenckhaus (1928). Lacassagne and others (1922).

77. Kennedy and Grover. Arnold. den Hoed and others. Minot and Spurling. Amundsen. Thomas and Bruner. Aubertin and Beaujard (1905 and 1908). Wegelin. Langendorf. Moldawsky. Mardersteig (1937). Gallavresi.

78. von Jagić and others. Carman and Miller. Evans and Roberts. Davey and Whitby. Weitz. Nielsen. Haagensen. Weil and Lacassagne. Béclère. Weil (1937). Laubry and Marchal. Maingot and others. Vaquez. Lavedan, cited by Aubertin (1932). Znajewska.

irradiation of lymphatic tumors.[79] The 24 victims ranged in age from 29 to 53 years; 20 were men and 4 were women. All had had years of occupational exposure to radiation, and several showed radium or roentgen burns of the hands. In 4 of the cases leukemia followed exposure to radioactive substances, and in the remaining 20 it was described as occurring in roentgenologists, radiologists and their assistants, who presumably had been working with roentgen rays. In 7 of the cases the condition was diagnosed as lymphatic and in 13 as myelogenous leukemia; in 4 the type was not specified.

The disease in these patients did not differ in character and course from spontaneous leukemia. Three patients were dead within six weeks and 10 within eighteen months; 3 lived four, five and six years, respectively; in 8 cases the duration of the disease is not stated. Only 3 autopsies are described,[80] and many of the reports give such scanty details that the authenticity of the cases is open to question. Two additional cases have been excluded because the relationship between the exposure and the leukemia was so vague (Merklen and co-workers; Rimbaud and co-workers).

A report from Weitz and one from Maingot, Girard and Bousser are of peculiar interest since each presents a detailed case history with repeated routine blood examinations covering a period of years before, during and after the development of leukemia. These two reports are among the few observations of the evolution of a leukemic blood picture. Weitz's patient was a woman who had been a roentgen technician since 1928 and was under observation for a period of eight years beginning in 1930. During 1931 and 1932 her blood picture showed the benign changes common to many poorly protected radiologic workers: slight relative lymphocytosis with eosinophilia and slight monocytosis. Immature cells were absent at first, but myelocytes began to appear in small numbers in 1933; at this time the total white cell count ranged between 18,000 and 20,000. All roentgenologic work was stopped in June 1933. Nevertheless the blood changes were progressive, and a frankly leukemic blood picture was established in March 1934, six years after the beginning of exposure to radiation. The leukemic blood picture was present for a year before significant symptoms developed, and the patient died of myelogenous leukemia in 1938, four years after the diagnosis was made.

The patient of Maingot, Girard and Bousser was a 50 year old woman who had been working as a roentgenologic nurse for fifteen years before routine blood examinations were begun in 1923. During the next five years, repeated brief episodes of asymptomatic leukocytosis were observed

79. Stewart-Harrison. MacCallum. Flashman and Leopold. Evans and Leucutia.

80. Haagensen. Weil and Lacassagne. Znajewska.

without abnormal cells. Monocytosis (10 to 30 per cent monocytes) was present during this period, but the differential count was otherwise normal. Toward the end of 1928 brief leukopenia (white cell count, 4,400) gave way to permanent leukocytosis. From 1930 to 1932 the leukocyte count rose in an oscillating fashion, varying between 15,300 and 28,600 with no immature cells; the neutrophilic polymorphonuclear leukocytes constituted between 67 and 78 per cent of the total. The red cell count remained normal. In March 1933, frank myelogenous leukemia suddenly appeared; the white cell count was 53,200 with 13 per cent myelocytes. The patient was still alive at the time the paper was written in 1938. The authors submit a table of blood counts covering the ten years before the diagnosis of leukemia was made and five years during the course of the disease.

It is also worth while to cite the paper of Weil and Lacassagne, which recounts the history of two chemists who worked with radioactive substances for years in the same laboratory. They employed no protection against the substances they were handling and died within five days of each other, one of aplastic anemia and the other of myelogenous leukemia.

In addition to these case reports, there is further suggestive evidence that radiation may bear a causal relation to leukemia in some cases. Experimental work by Furth and others [81] demonstrated that the incidence of spontaneous leukemia in laboratory animals can be greatly increased by properly administered radiation. Poisoning with benzene,[82] indole [83] and other substances produces changes in the blood and hemopoietic organs very similar to those which follow irradiation. In sporadic cases such poisoning in both man and animals has terminated in leukemia.[84]

Doubt still exists as to the etiologic role of radiation in the development of leukemia in radiologists, but on the basis of experiments on animals, it appears probable that repeated exposures to small doses of radiation could serve as an exciting or precipitating cause of leukemia.

PLASMA

The data on changes produced in the blood plasma by radiation are copious but conflicting. Some of the confusion arises from the use of different laboratory animals as test objects. Dogs, rabbits, guinea pigs and rats differ markedly from man, as well as among themselves, in

81. Furth. Furth and Furth. Lignac. Hueper.

82. Mallory and others. Feller. Martland (1929). Industrial Poisons, War Gas and Leukemia, Queries and Minor Notes, J. A. M. A. **110**:1508, 1938. Chronic Industrial Benzene Poisoning, editorial, J. A. M. A. **114**:517, 1940. Hess.

83. Büngeler (1932 and 1933).

84. Mallory and others. Büngeler (1932 and 1933). Chronic Industrial Benzene Poisoning, editorial, J. A. M. A. **114**:517, 1940. Forkner.

behavior and metabolism (Friedemann; Wells). To give only one example, the rodents in general do not vomit, and thus they lack an important mechanism which in other mammals causes gross loss of fluid and chloride during radiation sickness.

Much of the older as well as of the modern work suffers from inadequacy of quantitative chemical methods, particularly in determinations of the cholesterol, sodium, uric acid and hydrogen ion concentration of the blood. Another source of trouble has been the scarcity of serial observations taken at different intervals of time after irradiation. A single blood chemical determination fixes only one point of the curve of a reaction, which is often biphasic, always progressive and usually variable with the dose of radiation.

Blood plasma represents a balanced system in which a change in one constituent modifies so many others that a simple and comprehensible response to radiation would scarcely be expected. No attempt will be made to review all the literature, but a sample of opinion will be given on each topic.

Water.—Little is known about the influence of radiation on the metabolism of water. It is a very difficult problem to attack experimentally, yet it lies at the root of any interpretation of quantitative data on other blood components. Any change in the concentration or the dilution of the blood directly alters the concentration of all the formed and unformed blood constituents.

Hydremia occurring during the first few hours after irradiation has been described.[85] The increase in blood water is generally attributed to a transient rise in the osmotic pressure of the blood brought on by a sudden flood of metabolites and organic breakdown products. The occurrence of hydremia has been deduced from such indirect evidence as a sudden decrease in hemoglobin content and red cell count or a decrease in the dry residue of the blood (Lambin, 1930; Schlaginweit and Sielmann). This evidence is not entirely convincing.

The early effects of radiation on water metabolism are not clearly defined, but many of the later effects are well established. After heavy treatment the fluid intake of the subject is reduced by a loss of desire to eat and drink, and the fluid output is often increased by vomiting, diarrhea and occasional fever with sweating. The internal economy of water is disturbed by edema in and around the cells of the irradiated part (Failla) and by local vascular dilatation (Kottmaier; Lazarew and Lazarewa). All of these factors tend to produce systemic dehydration and to limit the amount of fluid available for the urinary excretion of metabolites. Complete anuria is rare after irradiation, but the urinary

85. Kroetz (1924 *b* and *c*). Schlaginweit and Sielmann. Lambin (1930). Tsukamoto.

volume is generally decreased for several days (Cameron and McMillan; Dodds and Webster). In man dehydration is readily remedied by parenteral administration of fluids, but in the experimental animals, which supply so much of our data on blood changes due to radiation, such severe dehydration is often permitted to develop that anhydremia must frequently result.

Acid-Base Equilibrium.—Lange in 1915 suggested, mainly on clinical grounds, that acidosis was the probable cause of radiation sickness. Denis and Martin produced acidosis experimentally by irradiating rabbits and observed that these animals refused acidogenic food (oats) while eating freely of foods rich in alkaline salts (lettuce and celery). Ono also observed acidosis in rabbits but found that it was transitory, appearing two to four hours after irradiation and disappearing in one to two days. Hirsch and Petersen reported similar changes immediately after treatment in patients receiving therapeutic irradiation. The hydrogen ion concentration increased with an occasional slight lowering of alkali reserve. However, after twenty-four hours these relationships were reversed with a decreased hydrogen ion concentration and an increased alkali reserve. Early acidosis followed by alkalosis has been observed by a number of other workers.[86] Liechti (1926), Ono and Magath, using different methods, all found increased local acidity in irradiated living tissue. Paralleling these observations, von Pannewitz found an increased hydrogen ion concentration in blood serum irradiated in vitro, and Arnow (1935) showed that solutions of egg albumin at an initial p_H of 7.46 were brought to p_H 4.78 by direct exposure to radon.

Little work has been done on the effect of differences in hydrogen ion concentration on the radiosensitivity of biologic material. However, it is well established (Arnow, 1936) that certain protein solutions in vitro are more readily flocculated by radiation, at a p_H near their isoelectric points (more acid than normal blood). Zirkle has shown that paramecia are more radiosensitive than normal in a slightly acid environment. Marshak found that weak concentrations of base decreased the percentage of abnormal mitoses in irradiated bean seedlings, and Uhlmann stated that an acidogenic diet increases the radiosensitivity of rabbits' skin.

It appears from this work that tissues are more vulnerable to radiation on the acid side of their normal reaction and that one of the initial effects of radiation on living tissues is to produce temporary acidosis. However, such views are strongly opposed. Bonanno (1934) found that rabbits on an alkaligenic diet suffered greater blood damage after irradiation than those on an acidogenic diet. Doub, Bolliger and Hartman, in an extensive series of experiments on rabbits, dogs and patients, failed to

86. von Pannewitz. Guthmann and Wirz. Kroetz (1924 *a* and *c*). Lacassagne and Loiseleur.

demonstrate early acidity and found, on the contrary, an alkaline change in both the tissues and the blood within an hour after irradiation. Their views have been supported by a number of other workers who reported increased blood alkalinity at various periods after irradiation.[87]

The immediate changes in blood and tissue acidity are of the greatest theoretic significance in unraveling the mechanism of action of radiation on biologic material. From the practical point of view, changes in the acidity of the circulating blood are of much less importance. Most observers find that routine radiation therapy produces insignificant fluctuations in blood p_H.[88] Those changes which have been observed cannot as yet be correlated either with the appearance of radiation sickness or with the ultimate prognosis of the patient (Woodard and Downes).

Sodium Chloride.—Evaluation of the effect of radiation on the blood sodium and chloride is complicated by the vomiting and diarrhea which may accompany radiation reactions. Large quantities of chloride are lost in vomiting, and diarrhea greatly increases the output of both chloride and sodium. Reports which do not consider these factors must be accepted with some reserve.

The blood sodium is reported both as rising (Kroetz, 1924 b, c) and as falling (Adler and Adler, 1931) after irradiation, but the reports on blood chloride are in better agreement. With few exceptions (Dodds and Webster), the authors describe decreased urinary excretion of chloride and chloride retention for the first few days after irradiation.[89] Associated with chloride retention, an early fall in the blood chloride is reported.[90] These findings immediately suggest that the data on excretion are in error and that excess chloride is really being put out undetected in the stools, vomitus, sweat or urine. Some of the reports, however, represent careful work and cannot be so easily discounted as erroneous. If one accepts them as true, the findings indicate either that chloride must be stored in the tissues after irradiation or that the total blood volume must be increased. Schlaginweit and Sielmann expressed the belief that the fall in blood chloride is due to dilution of the blood, but Beutel and Winter actually determined the tissue chlorides on 7 rats at intervals of one to eight days after total irradiation with 750 r to 1,000 r. Of the sixteen different tissues examined, all except the liver showed an increased chloride content on the basis of wet weight. Parallel charts of percental dry weight are given.

87. Pagniez and others. Kolta and Dunay. Kolta and Förster. Hussey.

88. Woodard and Downes. Graham. Konrich and Scheller.

89. Cameron and McMillan. Cori and Pucher. Engelhard and Sielmann. Loiseleur and Van Der Schueren.

90. Andersen and Kohlmann. Schlaginweit and Sielmann. Kroetz (1924 *b* and *c*). Kolta and Förster. Cameron and McMillan.

It is not possible to determine the importance of disturbed chloride metabolism in human reactions to radiation. It is reported that administration of chloride benefits patients with radiation sickness (Cameron and McMillan) even though many patients with and without radiation sickness maintain normal levels of blood chloride after irradiation (De Niord and co-workers; Graham).

Calcium.—There are practically no data on the calcium content of bones as affected by roentgen radiation. Internal administration of radioactive material, however, causes a resorption or decalcification of the bones of experimental animals.[91] Adler and Wiederhold found that the skin may lose as much as 57 per cent of its calcium after exposure to roentgen rays (1,000 r to 5,000 r). Heilbrunn and Mazia, after a brief review of the somewhat meager literature, found themselves in cautious agreement with the observations which show that calcium is set free from plant and animal tissues that have been irradiated with either radium or roentgen rays. Excessive excretion followed by retention of calcium has been described after irradiation (Adler and Adler, 1932), as well as late deposition of calcium in irradiated tumors and normal tissues.[92]

If tissue calcium is released in significant quantities soon after irradiation, one might expect a rise in the blood calcium, and a slight but definite rise has been reported (Andersen and Kohlmann; Zunz and La Barre). Other workers have found, to the contrary, that the blood calcium falls (Adler and Wiederhold; Doub and co-workers, 1925a). An early increase followed by a decrease is reported (Langeron and co-workers, 1931b), and still others have expressed the belief that radiation produces no significant alteration (Craver and MacComb; Jackson and Taylor).

A careful set of serial determinations might reveal that these discordant results are only in apparent conflict. If calcium is released from the tissues as an early reaction to radiation and subsequently is redeposited, the blood calcium levels might easily fluctuate on either side of normal, depending on the dose of radiation and the time at which the determinations are made.

The blood level of calcium hinges on innumerable variables other than those mentioned, and in healthy persons is held constant within narrow limits. The changes reported after irradiation are of some theoretic interest but are so small and so inconstant that they are hardly of great clinical importance.

Phosphorus.—Significant amounts of phosphorus are released from destroyed cells following heavy therapy and increased excretion of phosphorus commonly occurs, especially if a radiosensitive tumor or

91. Thomas and Bruner. Rosenthal and Grace. Flinn.

92. Kluge and Zwerg. Melnick and Bachem. Meltzer and Kühtz.

leukemia has been treated.[93] A corresponding increase in the blood phosphorus takes place in some patients [94] and may explain in part the vagaries of the blood calcium levels. Buckman and co-workers found that, in addition to an increase in total blood phosphorus, certain leukemic patients show a change of the phosphorus partition between the cells and the plasma. Alteration in the total blood phosphorus level is by no means a constant finding after irradiation,[95] and when present is usually of brief duration.

Cholesterol.—In vitro experiments show that cholesterol when dissolved in blood serum or in proper artificial solvents [96] may be partially decomposed by radium or roentgen rays and that postmortem irradiation of skin decreases its cholesterol content (Wile and co-workers). However, there is no agreement on the behavior of the blood cholesterol of laboratory animals or of patients after irradiation. Burgheim and also Mattick and Buchwald observed early decreases in blood cholesterol in practically all of their patients, while De Niord and co-workers found increases in the majority (61 per cent). Schumacher and Rusch and also Pohle, working with human beings, and Pohle and Sevringhaus, working with dogs, report numerous variations but no consistent trend of blood cholesterol after irradiation.

The wide and rapid fluctuation of blood cholesterol in normal subjects complicates the interpretation of any changes observed after irradiation. The only conclusion that can be drawn from the extensive literature is that no clearcut effect has been demonstrated.

Sugar.—In all species, the blood sugar fluctuates within wide physiologic limits, and there is a common hyperglycemic response to fear, excitement, rage, physical injury and carbohydrate ingestion. The most consistent change in blood sugar seen after irradiation has been the hyperglycemia observed in rabbits by several experimenters.[97] Engelbreth-Holm pointed out that this species is particularly liable to nonspecific variations in blood sugar and that in his own experimental work he believed the observed changes were in part artefactual. In dogs and human beings various degrees of hypoglycemia [98] and hyperglycemia [99] have been observed following irradiation.

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93. Ordway and others. Cori and Pucher. Knudson and Erdos. Loiseleur and Van Der Schueren. Warschawskaja.

94. Buckman and others. Doub and others. Kroetz (1924 *b*).

95. Jackson and Taylor. Craver and MacComb. Sprunt.

96. Löw-Beer. Roffo and Degiorgi. Reinhard. Macfate and Bache.

97. Rother (1924 and 1927). Tsukamoto. Lüdin. Kotschneff.

98. Rabboni. Lapatsanis. Langeron, Desplats, Paget and Chérigié. Rother (1924).

99. Nürnberger (1921). Rother (1924). Kolta and Förster. Kotschneff.

Numerous procedures have been reported as modifying the blood sugar response to irradiation in different animals. Among these are starvation (Lüdin; Rother), administration of atropine (Lüdin; Rother, 1924) or ergotamine (Rother, 1927), extirpation of the adrenals (Rother, 1924), section of the splanchnic nerves (Rother, 1927) and selective irradiation of the upper part of the abdomen (Rother, 1924), pancreas (Petersen and Saelhof), adrenals (Rother, 1924) and liver (Rother, 1924; Tsukamoto).

Brøchner-Mortensen, in an excellent attack on the problem in so far as it relates to human beings, found normal values for the blood sugar during fasting in patients throughout a course of roentgen therapy and a normal dextrose tolerance curve immediately after heavy treatment. Taylor and Jackson reported similar results. Most authors agree that there is no marked or consistent alteration of blood sugar in man which can be directly attributed to therapeutic irradiation.[100]

Nitrogen.—Hall and Whipple, McQuarrie and Whipple, Doub and co-workers (1925a) and Tsukamoto demonstrated that lethal doses of roentgen rays applied to the abdomens of laboratory animals produced a consistent rise in the urinary excretion of nitrogen and a later increase in the nonprotein nitrogen of the blood. Similar results have been obtained with therapeutic doses in man,[101] particularly in conditions such as leukemia or lymphoma, in which a considerable quantity of tissue is abruptly destroyed. However, most patients undergoing radiation therapy do not show any significant or consistent rise in the blood nonprotein nitrogen,[102] and in many there is no change seen in the urinary excretion.

These findings are compatible with what is known of the process of cell damage by radiation. Even heavy exposure of most normal tissues and the more radioresistant tumors does not result in sudden lysis of cells but rather in gradual dissolution extending over days and weeks. Under these conditions no marked rise in blood nitrogen would be expected, and any increase in the daily excretion of nitrogen would be slight. Another possible fate for some of the products of protein breakdown is suggested by the reported increase of blood amino acids after irradiation (Tsukamoto). In this form nitrogen might be reutilized by tissues without disturbing the nitrogen balance.

Many detailed examinations of blood and urine have been made for nonprotein nitrogen, urea, creatinine, creatine and uric acid,[103] as well as

100. Hirsch and Petersen. Brøchner-Mortensen. Kolta. Graham.

101. Schmitz. De Niord and others. Forkner. Warschawskaja.

102. Doub and others (1925 *a*). Hirsch and Petersen. Craver and MacComb. Graham. Breitländer and Lasch.

103. Cori and Pucher. Craver and MacComb. De Niord and others. Dodds and Webster. Doub and others. Hall and Whipple. Hirsch and Petersen. Matthews and Mazzola. Pohle and Sevringhaus. Schmitz. Tsukamoto. Warschawskaja.

for albumin, globulin, amino acids and various proteins,[104] in an attempt to discover some constant alteration in nitrogen metabolism attributable to radiation. The results of these determinations are not in complete agreement but do permit certain tentative conclusions. Small doses of radiation seldom produce any observable change in nitrogen metabolism. Moderate to large doses are frequently followed by significant increases in the nitrogen excreted, beginning as a rule some twenty-four hours after treatment. This effect is subject to considerable individual variation, both among human beings and among laboratory animals, but is most marked after heavy exposure of the abdomen. The nitrogen content of the blood is less readily affected by radiation than the urinary output (Hall and Whipple) but in certain cases shows a significant increase at some time within a week after treatment. When the blood nonprotein nitrogen does rise, the increase, as would be expected, is made up largely of uric acid and urea.[105] There is also a significant increase in the amount of unidentified nitrogenous material (Schmitz), possibly purines (Doub and co-workers; Hall and Whipple).

There is an insufficient amount of data on changes in the total plasma proteins, globulin, euglobulin, albumin or amino acids [106] to warrant any conclusions, but the changes, if any, are small. Several observers have reported an increase in blood fibrinogen following irradiation.[107]

Unfortunately, a great deal of laborious work in this field is rendered inconclusive by the lack of determinations of renal function. Renal insufficiency would limit excretion of nitrogen and favor an increase in blood nitrogen. On the other hand, radiation therapy in such conditions as cancer of the cervix or of the bladder often improves renal function by relieving ureteral obstruction, thus favoring increased excretion and decreased retention of nitrogen.

COAGULATION TIME

Agreement is general that radiation shortens the coagulation time of the blood. The coagulant effect was described in 1920 by Stephan, who successfully treated a patient for purpura fulminans by irradiating the spleen. Subsequent work has demonstrated that the coagulation time is shortened in 30 to 80 per cent of persons and animals after irradiation with small or moderate doses.[108] In any particular case

104. Tsukamoto. Held and Hülbach. Breitländer and Lasch. Davy. Gaessler. Knipping and Kowitz. Kroetz (1924 *c*). Saelhof.

105. De Niord and others. Schmitz. Matthews and Mazzola. Doub and others. Warschawskaja. Tsukamoto.

106. Breitländer and Lasch. Gaessler. Tsukamoto. Knipping and Kowitz. Doub and others. Kroetz (1924 *c*). Davy.

107. Held and Hülbach. Knipping and Kowitz. Frisch and Starlinger.

108. Lavedan. Pagniez and others (1924 *a* and *b*). Petersen and Saelhof (1921). Elving. Canuyt and Wolf. Kolta and Förster. Lapatsanis. Carman and Miller. Nürnberger (1923). Jansen and Schultzer. Saelhof. Frisch and Starlinger.

the decrease in coagulation time may be slight or it may amount to as much as 50 per cent (Canuyt and Wolf; Pagniez and co-workers, 1924a). Some persons in each series fail to show any change, but only rarely is the clotting time prolonged [109] unless massive doses have been administered. Pagniez, Ravina and Solomon (1924b) found that in 20 of 24 patients the coagulation time of blood drawn a few minutes and one hour after delivery of 2.5 Holtzknecht units of roentgen rays was definitely shortened. The same authors (1924a, b) found that the result was the same no matter what part of the body was exposed. The rate of appearance and disappearance of this effect is not thoroughly worked out. Stephan expressed the belief that the coagulation time reached a minimum at two to four hours after treatment; Pagniez and co-workers (1924b), at one to four hours; Elving, at about four hours, and L. Nürnberger at three days. Coagulation is reported as returning gradually to normal after eight hours (Elving) and also in four to seven days. The coagulant properties appear to be unchanged by irradiation of blood in vitro (Pagniez and co-worker, 1924b). Several workers have reported a rise in blood fibrinogen after irradiation.[110] Saelhof determined quantitatively the platelets, prothrombin, fibrinogen and antithrombin of dogs after irradiation of the hepatic, the splenic and the intestinal regions of the abdomen. The individual factors varied in different directions, depending on the region exposed, but in all cases the combined effect was to shorten coagulation time as tested one-half, one, five and twenty-four hours after treatment.

Radiation may have a certain usefulness in the clinical treatment of such hemorrhagic conditions as menopausal or functional uterine bleeding (von Massenbach; L. Nürnberger) or purpura.[111] In such attempts, treatment is generally applied to the splenic region. The effects, however, are inconstant (Partsch), and other types of therapy are more widely employed.

SEDIMENTATION RATE

Bonanno, in a review of some of the factors affecting the sedimentation rate of erythrocytes, discussed the effects of irradiation. He found little agreement in the literature and studied 37 irradiated patients of his own. He concluded that the observed changes were inconstant and transient. The commonest change was a brief acceleration of the rate, and this generally followed exposure of the abdomen or other vascular regions. Heilbrunn and Mazia in 1936 again briefly reviewed

109. Pagniez and others. Zunz and La Barre. Bernhard.

110. Held and Hülbach. Frisch and Starlinger. Knipping and Kowitz.

111. Jones and others. Garland. Goldmark and Jacobs. Mettier and Stone. Pancoast and others.

the conflicting evidence and reached no conclusions. None of the many articles published on the subject appear to offer conclusive evidence of any consistent effect.

BLOOD PRESSURE

A good many observations have been made on the blood pressure of patients after irradiation. The common conclusion is that the majority of persons show a transient decrease in systolic pressure, diastolic pressure or both.[112] The drop may occur immediately after treatment (Panow, Schroeder) or gradually over several hours (Panow; Wolmershäuser). In general, the blood pressure returns to its previous level within a few days (Panow) but occasionally remains depressed for weeks (Schroeder; Wolmershäuser). Pfahler found that mild chronic hypotension is a common condition among radiologists.

Some physicians have hoped to relieve high blood pressure by irradiating the adrenal regions, but the effect on blood pressure appears to be the same whether the adrenals are included in the direct field or not (Desjardins and Marquis). Desjardins (1932b), in an able review of the subject, concluded that no direct effect of radiation on blood pressure has been demonstrated and that the observed changes are probably secondary to the general systemic depression which so commonly follows treatment. In keeping with this conclusion, clinical experience has generally shown that radiation is an ineffective means of controlling hypertension (Yater and co-workers).

IMMUNOLOGIC SUBSTANCES AND REACTIONS

Scattered work has been done on the immunologic aspects of radiation reactions. It has been found that even very heavy irradiation of antigens in vitro does not alter their antigenic specificity (Ling) and that doses far in excess of 10,000 r are necessary to produce any detectable destruction of antibodies in vitro (Fricke). Similar massive doses have been reported as producing some reduction of the toxicity of diphtheria and other toxins (Brooks; Fabre and Ostrovsky), as well as partial or complete inactivation of various snake venoms (Phisalix), bacteriophages (Baker; Wright and Kersten), viruses (Baker; Gowen and Price), and complement (Brooks; Cori; Lusztig).

Baker arranged some of these materials in the order of their increasing resistance to destruction by beta radiation as follows: Escherichia coli, Staphylococcus aureus, vaccinia virus, bacteriophage, filtrate of Rous sarcoma 1, tetanus toxin, Bacillus anthracis spores, hemolytic amboceptor, guinea pig complement, trypsin, lysozyme, pepsin and invertase. Most of these results were obtained in vitro with doses of radiation far beyond the therapeutic range. The experimental work done

112. Desjardins and Marquis. Schroeder. Wolmerhäuser. Yater. Carman and Miller. Panow.

on living animals has raised many interesting questions but answered few of them. It is generally agreed that radiation, even up to the lethal limit, has little effect on preformed circulating antibodies but that sublethal radiation administered near the time of injection of an antigen may seriously impair production of antibodies, presumably by injuring reticulo-endothelial tissue.[113]

The effect on circulating complement is less certain. Cori and Heeren noted departures from the normal range of complement titer in the blood of patients under therapeutic irradiation. The titer was altered either up or down without relation to the dose of radiation administered, and then returned gradually to its preirradiation level. In animals an increase in complement has been reported after small doses (Manoukhine; Quadrone) and a decrease after larger ones (Lusztig; Quadrone). Petersen and Saelhof (1921) found no change in the complement titer, and Brooks in a brief review concluded that the experiments so far reported are in no instance conclusive.

An undefined "toxicity" of blood is described as a result of irradiation of blood or serum either in vivo or in vitro. This toxicity is said to show itself in a number of ways. Among them are (1) an impairment of the growth of root tips immersed in irradiated serum (Macht; Macht and Hill), (2) a leukopenic action of irradiated blood or serum when injected into animals or man,[114] (3) the production of toxic symptoms by injecting irradiated blood (Tsukahara), (4) the death of a normal animal having cross-circulation with an irradiated animal (Zacherl) and (5) the destructive effect of local irradiation on distant tissue (Ssipowsky). Among the evidence against the presence of any such toxic material is the observation made at Strangeways Research Laboratory, in Cambridge, England, that extracts of irradiated chick embryos do not impair the growth of tissue cultures (Spear).

Some authors have claimed that a "leukolytic agent" found in the blood of irradiated subjects can be destroyed by heating the blood to 55 or 60 C. (Curschmann and Gaupp). Blood heated to this temperature is partially broken down (Isaacs and co-workers) and on injection might affect the blood counts quite independently of the presence or the absence of any preexisting "leukolytic agent."

The reported toxicity of irradiated blood is usually explained as a result of the release into circulation of proteins or protein breakdown products from damaged tissue. If such were the case one might expect to see the blood protein or the blood nonprotein nitrogen increase after irradiation. This effect has been observed as described in the section

113. Colwell. Brooks. Benjamin and Sluka. Hektoen. Läwen. Simonds and Jones. Fränkel and Schillig. Hempel. Paulin.

114. Woenckhaus (1936). Linser and Helber. Strumia. Curschmann and Gaupp. Capps and Smith. Tsukahara.

on nitrogen but is seen mainly in experimental animals in the terminal stages of fatal radiation toxemia. No consistent change is seen in the blood nitrogen of patients after ordinary radiation therapy.[115]

Of course, protein breakdown products might be toxic in concentrations too small to be detected by the methods of blood chemistry. Any of the higher protein degradation products, particularly if toxic, might possibly act as endogenous antigens and stimulate the production of antibodies. It would then be reasonable to expect that repeated irradiation might result in immunity against radiation toxicity or perhaps in an anaphylactic reaction. Neither of these effects has been observed. Cappelli, investigating the hypothesis by immunologic methods, was unable to obtain any flocculation on using as antigen the serum of rabbits taken a few hours after heavy irradiation, and as antibody serum from rabbits which had recovered from fractionated roentgen treatment. Mischtschenko and Fomenko, on the other hand, claimed that they had demonstrated antibody production by endogenous antigens derived from radiation breakdown of tissue proteins. Protein antigens were prepared from the liver, kidney and muscle of normal animals. In the experimental animals corresponding organs were treated with 20 to 100 per cent of an erythema dose of roentgen rays. The serums of the irradiated animals when tested against the prepared antigens showed complement fixation. The authors found that 60 per cent of an erythema dose produced the maximum effect. The Wassermann reaction in these animals remained negative, although Malfa and Basco found that in syphilitic persons radiation applied over the splenic area fortified a weakly positive Wassermann reaction or reversed a false negative one. Brann found that irradiation of human blood in vitro had no effect on the Wassermann reaction except for occasional slight weakening of a positive reaction.

The effect of radiation on phagocytosis has been the subject of considerable investigation. Knott and Watt found that the leukocytes of normal and leukemic blood irradiated in vivo or in vitro showed a loss of their ability to phagocytose staphylococci, and Schönig noted that the rate of removal of congo red from circulation was decreased in irradiated patients. Schwienhorst, working with rats, observed microscopically that after heavy irradiation the reticuloendothelial cells were damaged and that phagocytosis by cells lining blood channels was decreased. As a result, killed staphylococci injected into the blood stream remained in circulation longer in these rats than in control animals. Benjamin and Sluka found that injected protein antigens remained in circulation much longer in heavily irradiated rabbits than in controls. Pohle, Koga and Teneff and Stoppani, using very small doses (42 to 150 r), demonstrated an increased storage of injected pigment by the reticuloendo-

115. Hirsch and Petersen. Craver and MacComb. Breitländer and Lasch.

thelial cells at various times after irradiation. The latter two authors found that while small doses of radiation increased the phagocytic function, moderate doses impaired it and large doses destroyed it. Chrom (1937), however, was unable to demonstrate any change in the rate of removal of injected bacteria from the blood stream of mice after local or general irradiation with 10 to 75 r.

Schürer pointed out the importance of the time factor in work of this kind. His own experiments showed that phagocytosis was inhibited (reticuloendothelial blockade) during the first four hours after exposure to roentgen rays but that eight hours after treatment this condition had given way to one of increased phagocytic activity.

An increase in the bactericidal action of the blood of both men and animals is claimed by several authors as a response to small doses of roentgen radiation.[116] It is not always made clear whether this change represents an effect on opsonins, on leukocytes, on antibodies or on the direct toxicity of the serum. If any such effect occurs regularly, it is of the greatest interest and deserves to be more completely defined.

Bacteria themselves are enormously radioresistant in artificial culture, surviving doses of 25,000 to 100,000 r, when roentgen rays are used, and comparable exposures to radium.[117] An increase in volume of irradiated bacteria has been described (Dietz) similar to the reported imbibition of fluid by irradiated red cells (Koch; Woodard). Fiorini and Zironi were unable to detect any effect of roentgen radiation on the agglutinability of Bacillus typhosus as tested with specific agglutinins.

Heavily irradiated animals and human beings show increased susceptibility to bacterial infections,[118] but small doses appear to have a definitely favorable effect on the response to some infectious processes.[119] Doses of 25 to 200 r are found most effective, while larger doses impair the healing process. No satisfactory explanation of these effects has ever been given. Doses of less than 200 r could scarcely be expected to damage bacteria directly. Several authors propose that the leukocytes surrounding an inflamed area may be broken down even by such small doses and loose their lytic ferments to destroy the invading bacteria. If this were the main mechanism involved, one would expect heavier doses to enhance rather than destroy the beneficial effect. If one seeks some other explanation, one is left with an undefined increase in bactericidal action of the blood, a possible increase in phagocytic activity of reticuloendothelial cells and a questionable nonspecific protein-like effect (Pfalz). None of these appear adequate to explain the prompt healing of certain infectious processes after light irradiation.

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116. Holzknecht (1926). Fried (1925 *a* and *b*). Pfalz. Brooks.

117. Klövekorn. Duggar. Baker.

118. Chrom (1935). Cramer and others. Läwen. Colwell.

119. Desjardins (1939 *c*). Pordes (1929). Fried (1925 *a* and *b*). Holzknecht (1926).

HEMOPOIETIC ORGANS

Damage to blood-forming organs appears to be the chief cause of changes in the blood picture after irradiation. The best single criterion of the functional integrity of the blood-forming organs is the maintenance of a normal blood picture, but a thorough appraisal of the state of the hemic system requires parallel histologic studies of the bone marrow and lymphatic tissue.

Several difficulties complicate the correlation of these studies. The blood-forming organs have such a large reserve capacity that minor degrees of damage may not be reflected in the circulating blood; the cellularity of the bone marrow and the lymphatic organs is not a dependable indication of the number of cells being delivered to the circulation, and the reaction of the marrow to injury is often irregularly distributed, so that a single microscopic section may give a false impression. Even more important is the natural delay in the manifestation of hemopoietic damage in the circulating blood. Each of the types of blood cells has a different life expectancy. Lymphocytes are believed to survive in circulation for only a brief period, granulocytes for a week or more and red cells for some six weeks. Thus, complete cessation of all new blood cell formation would theoretically result in an abrupt drop in blood lymphocytes, a more gradual fall in granulocytes and a leisurely decline in red cells. Just such a sequence is seen after very heavy irradiation, and the inference has often been hastily drawn that the rate of decrease of the cells of each type is a direct indication of their radiosensitivity. It is probable that the lymphopoietic, granulopoietic and erythropoietic tissues do fall into this order of radiosensitivity but that the quantitative differences are not nearly so great as might be inferred from the blood counts. These facts explain in part the difficulty of demonstrating synchronous parallel changes in the blood and the blood-forming organs.

It is well established that the most severe radiation damage is suffered by those hemopoietic organs lying within the field of treatment. Animal experiment has repeatedly shown that bone marrow and lymph nodes outside the field are also affected.[120] The reaction outside the field of treatment appears a little later, is not so intense and returns to normal more rapidly than the local changes but shows the same characteristic early cell destruction, phagocytosis and subsequent atrophy or hyperplasia that may be seen within the treated regions.

The distant effect of radiation locally applied has never been adequately studied on human material. Many radiologists have noted clinically the striking distant effects of local irradiation in Hodgkin's disease, lymphoma and leukemia. Bertola and co-workers made biopsies

120. Ssipowsky. Aubertin and Beaujard (1905). Akaiwa and Takeshima. Siciliano and Banci-Buonamici.

of bone marrow from 10 patients with leukemia or Hodgkin's disease and from 4 normal persons after exposure to doses of 60 to 630 r. Changes were induced in the sternal marrow of 2 leukemic patients by irradiation of the spleen alone. Den Hoed and co-workers found remarkable alterations in the marrow and spleen at the autopsies of 4 patients who had received 715, 475, 550 and 525 r, respectively, to all or most of the body surface in periods of thirteen to thirty-one days. The marrow changes in all cases were far in excess of what might be expected to follow local irradiation of the marrow with comparable doses. Thus, the extensive destruction of marrow seen in 3 cases and the reactive hyperplasia seen in the fourth case must be attributed in part, at least, to the indirect effect of radiation absorbed by other parts of the body.

There is no reliable means of assessing the relative importance of direct and indirect hemopoietic damage in ordinary radiation therapy, but it is well to keep in mind that massive therapy to any part entails some damage to lymphatic organs and marrow all over the body.

The degree of damage, both local and general, is roughly proportional to the size of the dose of radiation. Small single doses rarely produce irreversible injury; larger doses, particularly if repeated or applied to large fields, produce permanent hypoplasia; regenerative hyperplasia is seldom seen except as a late result of repeated or continuous exposure to low intensities. The wide individual variations in response make it impracticable to define these ranges of dosage more exactly.

The studies about to be described on the response of marrow and lymphatic organs to radiation have been carried out for the most part on small laboratory animals. The general character of the changes seems to be very similar in the different species and corresponds quite well with the scanty data on human beings. Therefore, no attempt has been made to segregate results obtained on different species.

Bone Marrow.—The marrow is generally observed to be more resistant to radiation damage than the lymphatic tissue.[121] Tsuzuki found that 12 per cent of an erythema dose produced definite changes in the marrow of rabbits and ten Doornkaat Koolman reported alterations in local and distant marrow in dogs after one third of an erythema dose had been applied three times to one limb. It appears from the work of Mayneord and Piney that repeated exposures may produce more lasting damage to marrow than large single doses. This furnishes an interesting parallel to the effectiveness of the fractional treatment of tumors.

Differential cell counts on the marrow of irradiated rats (Lingley and co-workers) and rabbits (Wünsche) have shown an early relative and an absolute decrease in the numbers of normoblasts and other

121. Heineke (1905). Jolly (1924 *b*). Tsuzuki. Lacassagne and Lavedan (1924). Mayneord and Piney.

immature cells and an increase in the segmented granulocytes. Recovery was rapid after small doses, but larger doses led to progressive damage and hypoplasia. The rapid changes in the marrow picture revealed by these serial counts illustrate the danger of generalizing from isolated observations.

Heineke (1905), who did some of the earliest and best experimental work on this problem, found well marked destruction of marrow cells within three hours after irradiation, maximum destruction in about eleven hours and early regeneration in five to six days, with complete recovery at the end of three to four weeks. After moderate doses, the initial nuclear destruction and fragmentation are apparent twelve to twenty-four hours after treatment (Jolly, 1924b; Ssipowsky) and affect principally the young cells of the granulocytic series. Erythroblastic foci of normal appearance may persist in the face of considerable damage to other cells[122] but do show evidence of injury after heavier or repeated treatment (den Hoed and co-workers; Lacassagne and Lavedan). The megakaryocytes are among those cells which show early degenerative changes (Ssipowsky). They are usually damaged or reduced in number whenever other elements in the marrow show signs of injury.[123] Two days after irradiation mitotic activity in the marrow is depressed (Mottram, 1920b), but within a week after sublethal irradiation some evidence of regeneration is shown in the increased number of mitotic figures in cells of all series (Heineke, 1905; Jolly, 1924b). At the same time destruction and fragmentation of cells and phagocytosis of debris may continue (Heineke, 1905; da Silva-Mello). The end result may be a gradual return to a normal marrow picture, partial repair resulting in an immature, hypoplastic marrow (den Hoed and co-workers; Wegelin) or progressive injury going on to aplasia and death (Heineke, 1905; Shouse and co-workers). In some cases regeneration continues for weeks or months (Heineke, 1905; Casati) after destructive changes have disappeared and leads on to the formation of hyperplastic marrow crowded with young cells, sometimes described as belonging predominantly to the granulocytic series (Aubertin and Beaujard, 1908; Rosenthal and Grace) and sometimes to the erythroblastic series.[124] Rosenthal and Grace found that in rabbits poisoned with radium early erythroblastic hyperplasia is replaced by later myelocytic hyperplasia. The hyperplasia is not confined to regions of normal hemopoiesis but may extend well down into the shaft of the

122. den Hoed and others. Milchner and Mosse. Aubertin and Beaujard (1905). Vallebona and Capocaccia. Jolly (1924 *b*). Heineke (1905).

123. den Hoed and others. Shouse and others. Jolly (1924 *b*). Lacassagne and Lavedan (1924). Heineke (1905). Siciliano and Banci-Buonamici. Ssipowsky. Thomas and Bruner.

124. Gendreau and Pinsonneault. Martland (1926, 1929 and 1931). Rosenthal and Grace. Reitter and Martland. da Silva-Mello.

femur [125] or the tibia (Gendreau and Pinsonneault) and even appear in the form of extramedullary foci of hemopoiesis in the spleen, lymph nodes or liver.[126] Scattered through the hyperplastic marrow are deposits of hemosiderin (Reitter and Martland), foci of cell-poor gelatinous edema and areas of fibrosis of varying density and size. The detailed histologic picture of full-blown hyperplasia, immaturity and focal fibrosis is best described by Martland (1931) as it occurred in a group of persons suffering from occupational ingestion of mesothorium, radiothorium and radium. Although this might be considered a special type of exposure, similar changes in the marrow may follow external application of roentgen rays.[127]

In most cases marrow which has been heavily irradiated does not show hyperplasia but in a short time becomes and remains cell poor (Ssipowsky). The normal cellular elements are replaced by loose, edematous connective tissue in which scattered islands of hemopoiesis and rare megakaryocytes survive (den Hoed and co-workers). The sinusoids become prominent because of the disappearance of other structures. Moderate eosinophil or plasma cell infiltration and hemosiderin deposits are sometimes present. These changes are nonspecific and produce a picture quite similar to that of the atrophic marrow occasionally seen in elderly people.

The histologic changes in the marrow are not completely reflected in the circulating blood. The red cell series shows the best correlation. Anemia is a late result of heavy irradiation but once established may be progressive. Similarly, the erythropoietic tissue, according to the majority of observers, shows considerable initial radioresistance, but once it is damaged its ability to recover is limited.

Study of the circulating granulocytes, on the other hand, sheds little light on what is going on in the marrow. The initial granulocytosis which follows twelve to twenty-five hours after irradiation corresponds to the reported increase of segmented granulocytes in the marrow. It also coincides with the first appearance of destructive changes and, according to Mayneord and Piney, represents mobilization of granulocytes rather than new formation of these cells in the marrow. The prolonged subsequent granulopenia in the blood stream covers the period during which regeneration is most active in the marrow and may continue even after the marrow has become definitely hyperplastic. This picture is comparable in some respects to that seen in pernicious anemia, in which the hyperplastic but immature marrow fails to deliver its cells

125. Martland (1925, 1926 and 1931). Ross.

126. Thomas and Bruner. Aubertin and Beaujard (1905). Rosenthal and Grace.

127. Gendreau and Pinsonneault. Aubertin and Beaujard (1905 and 1908). Pappenheim. Piney.

to the circulation. In both cases evidences of regeneration may be detected in the blood stream by the finding of young granulocytes and red cells. In those cases in which regeneration fails to take place and permanently hypoplastic marrow results, the peripheral blood picture may vary from normal to that of severe aplastic anemia, depending on the severity of the damage and the amount of marrow involved.

Lymphatic Organs.—Fixed lymphoid tissue throughout the body is highly radiosensitive and, like the circulating lymphocytes, it shows remarkable powers of recovery (Heineke, 1904; Jolly, 1924b). A few scattered lymphocytes almost always survive, even in heavily irradiated regions, and make some attempt at regeneration. Different estimates have been made of the amount of radiation necessary to produce histologic changes in lymphatic tissue. These range from the infinitesimal doses used by Murphy to about one third of an erythema dose (Akaiwa and Takeshima).

(*a*) Lymph Nodes: The early changes in lymph nodes have been studied almost exclusively in animals. Within an hour after roentgen treatment of rabbits with one third of a skin erythema dose (Akaiwa and Takeshima) and one to six hours after other doses in various animals,[128] degeneration of lymphocytic nuclei with breaking up of germinal centers is apparent. Some swelling of the node is seen together with congestion and exudation. During the next five days the lymphocytic destruction is progressive and macrophages appear in great numbers, devouring nuclear fragments and red blood cells.[129] During this stage, if the dose has not been too heavy, regeneration begins, even before the destructive changes are complete. Mitoses in the lymphoid elements are absent during the first few days but then become abundant, and the node may be largely replaced by huge germinal centers (Sabin and co-workers; Thomas and Bruner). After a heavier dose edema develops and sometimes hemorrhage.[130] In either case the gross dimensions of the node are increased for a short time, giving two possible explanations of the enlargement of lymph nodes sometimes noted a postirradiation change in man (Lange). If the dose has been small, the node returns in a few more days to its original size and structure (Heineke, 1904; Jolly, 1924b).

When treatments of one or more erythema doses are applied, the destruction of lymphocytes is more rapid and profound, and repair is delayed.[131] After massive treatment, the lymph nodes rapidly decrease

128. Jolly (1924 *b*). Warthin. Heineke (1904). Tsuzuki.

129. Akaiwa and Takeshima. Shouse and others. Clarkson and others. Tsuzuki. Jolly (1924 *b*). Heineke (1904).

130. da Silva-Mello. Krause and Ziegler. Shouse and others.

131. Akaiwa and Takeshima. Ellinger. Teneff and Stoppani. Ross.

in size due to destruction of most of the cells that make up their substance. Repair takes place chiefly by collapse of the node, with only slight formation of new connective tissue. The end result is a small, poorly defined mass of loosely woven connective tissue very difficult to identify as a lymph node except by the few lymphocytes that almost always survive. The lymphatic channels through such nodes are said to remain normally permeable to the lymph circulation (Teneff and Stoppani). The lymphoid deposits in the intestine, mesentery and other viscera show the same changes that are found in the lymph nodes.

(*b*) Spleen: There is some evidence that the radiosensitivity of the spleen increases with increase in its blood supply,[132] but in general the spleen is considered somewhat less radiosensitive than the lymph nodes. Destructive changes appear a little later than in the nodes and require somewhat larger doses, but regeneration is not so complete (Tsuzuki). Practically all of the lymphocytes in the spleen may be destroyed by massive irradiation. Many of the reticular cells of the red pulp are destroyed by these doses. Others become swollen[133] but survive and maintain the integrity of the organ.

Grossly, the spleen undergoes brief early swelling like the lymph nodes[134] and then shrinks rapidly. In rats and mice its weight is reduced to about one fourth of normal within a few days after irradiation with doses sufficient to cause delayed death (Clarkson and co-workers). In a few human subjects autopsy has shown the spleen enlarged after massive exposure (Reitter and Martland). Far more commonly the organ is shrunken and fibrotic and stained dark brown by deposits of iron pigment.[135]

Microscopically, the spleen resembles the lymph nodes in its response to radiation. The earliest visible changes appear two to six hours after treatment and consist of pyknosis and fragmentation of lymphocytic nuclei in the germinal centers of the malpighian bodies.[136] A few polymorphonuclear leukocytes appear almost at once in these areas of destruction but are soon replaced by enormous numbers of macrophages loaded with phagocytosed nuclear fragments and red blood cells.[137] Within a few days after heavy treatment the lymphocytes may have disappeared almost completely.[138] The malpighian bodies can be identi-

132. Poos. Jolly (1924 *b*). Holthusen (1925).

133. Schwienhorst. Heineke (1904). Ssipowsky.

134. Warthin. Tsuzuki. Krause and Ziegler.

135. Wegelin. Ross. den Hoed and others. Aubertin (1932). Gavazzeni and Minelli.

136. Heineke (1904). Warthin. Tsuzuki. Schwienhorst. Krause and Ziegler.

137. Shouse and others. Warthin. Tsuzuki. Ellinger. Heineke (1904). Thomas and Bruner.

138. Tsuzuki. Schweinhorst. Heineke (1904). Clarkson and others. Ellinger.

fied only with difficulty, the pulp appears cell poor and empty (Schwienhorst), and the sinusoids stand out clearly for a time (Harvey; Rosenthal and Grace) before they collapse.

A few weeks after exposure the spleen has reached a fairly stable state of repair. Most of the macrophages have disappeared. Some excess phagocytosis is still apparent and considerable deposits of hemosiderin remain.[139]

The malpighian bodies show little evidence of regeneration and are represented by a few lymphocytes clustered around the smaller arteries [140] —a picture quite similar to that of senile atrophy of the spleen. The fibrous tissue is proportionately increased,[140] principally by thickening and condensation of the preexisting trabeculae rather than by diffuse fibrosis (Heineke, 1904; Wegelin). Many plasma cells may be present (Ross; Thomas and Bruner). If the marrow has been severely damaged, islands of hemopoietic tissue are often found scattered through the pulp.[141] The effect of irradiation of the spleen on blood clotting has been discussed in the section on coagulation time.

A special form of exposure to radiation follows the parenteral introduction of thorium dioxide (thorotrast). This material emits mainly alpha radiation, and when injected in colloidal form it is picked up selectively by the reticuloendothelial cells of the spleen and other organs. It is said that in the spleens of rabbits and guinea pigs the thorium particles are found chiefly in cells at the center of the malpighian bodies, but in rats and mice, at the periphery (Tripoli). If the dose of injected thorium dioxide is large enough, degeneration of lymphocytes and splenic parenchyma follows much as it does after externally applied radiation. There is little evidence that the mere presence of thorium in the spleen enhances the effect of roentgen radiation (Gilbert and co-workers).

(*c*) Thymus: The thymus is probably intermediate between the spleen and the lymph nodes in radiosensitivity but shows some regeneration even after 90 per cent of its substance has been destroyed by radiation (Hughes and Job). Degenerative changes similar to those seen in lymph nodes appear in the thymus within two hours after treatment (Heineke, 1904; Jolly, 1924a). The organ may be reduced by heavy radiation to a fibrous mass containing only a few lymphocytes and many closely packed Hassall's corpuscles. The thymus apparently does not acquire deposits of iron pigment after irradiation as do the other lymphoid organs (Clarkson and co-workers).

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139. Wegelin. den Hoed and others. Reitter and Martland. Mayneord and Piney. Heineke (1903). Clarkson and others.

140. Ross. Wegelin. Thomas and Bruner.

141. Aubertin and Beaujard (1905). Thomas and Bruner. Rosenthal and Grace.

It has been proposed that the accumulation of hemosiderin in reticuloendothelial cells after irradiation might represent a failure of these cells to dispose of iron pigment in the normal manner rather than an excess phagocytosis of red cells (Lambin). It seems clear from the work cited earlier that excess phagocytosis of red cells takes place in the spleen and lymph nodes at least during the early phase of the reaction, although it is quite possible that the disposal of the resulting pigment may be delayed.

The lymphocyte count of the peripheral blood does not follow exactly the histologic changes in the lymphatic tissues. The initial lymphopenia corresponds quite well with the early destruction of lymphocytes, but the return toward normal progresses much more rapidly in the nodes than in the circulating blood. The blood at first reflects the regenerative process only by the appearance of a few immature lymphocytes.[142] The blood lymphocyte level in human beings returns to normal in one or two months after heavy irradiation, long after the lymphatic organs have reached a fairly stable condition of regeneration or aplasia.

SUMMARY

Routine radiation therapy seldom produces permanent or dangerous modifications in the blood. Sufficient irradiation of tissues with either roentgen rays or radioactive substances will cause a decrease in the number of cells of all series in the circulating blood as well as severe damage of the cells of the blood-forming organs. Larger doses lead to more profound and earlier damage with slower recovery. In extreme cases death may result from agranulocytosis, anemia or purpura. The total effect of radiation is roughly proportional to the dose and the size of the field exposed, but it also varies with the time during which the radiation is applied, the part of the body treated and the susceptibility of the subject.

The marrow and lymphoid organs show destructive changes after a brief period of latency. If the dose has been small, recovery is rapid and uneventful, but large doses may lead to permanent or progressive hypoplasia. In some instances the marrow may be found in a state of regenerative hyperplasia, especially after chronic exposures.

Radiation changes in the peripheral blood cells appear after various periods of latency but may then be progressive for months without further irradiation of tissues. The lymphocytes, polymorphonuclear leukocytes and red cells do not show a parallel response to any one technic of irradiation, but with proper adjustment of technic it has been

142. Thomas and Bruner. Portis. Amundsen.

possible to induce a similar response in each series independently. This response consists in an early rise above normal followed by a fall below normal and gradual recovery.

The number of cells of any type remaining in circulation at a given time after radiation treatment represents in part the natural survival period of that cell type and in part a balance between radiosensitivity and ability to recover from injury. The experience of the majority of workers has been that the blood cells most susceptible to injury enjoy the most rapid and complete recovery. The same rule probably holds true for the corresponding cell types in the hemopoietic organs. We may thus arrange the principal blood cells and hemopoietic tissues in a single series in the order of decreasing radiosensitivity and decreasing ability to recover from injury.

Lymphocytes and Lymphoid organs	>	Granulocytes and Granulopoietic tissue	>	Erythrocytes and Erythropoietic tissue

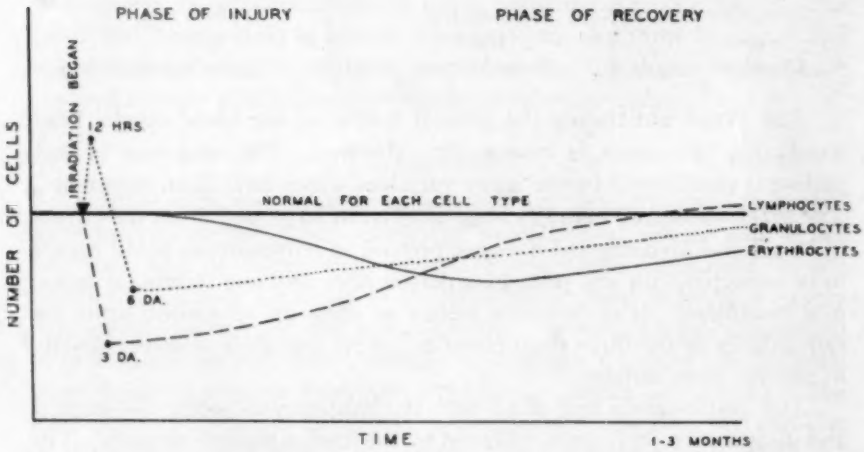
Any graph illustrating the general course of the blood counts after irradiation of tissues is necessarily arbitrary. The response of any patient is conditioned by the many variables which have been mentioned. The graph presented here has been adapted in large part from the curves of Minot and Spurling and does not pretend to represent the blood counts to be expected with any particular person after any one technic of radiation treatment. It is intended rather to show in simplified form the radiolability of the three main blood cell types and their relative capacity to recover from damage.

The graph shows that of all cells the lymphocytes suffer the earliest and most severe depression, followed by the most adequate recovery. The granulocytes are intermediate, while the erythrocytes suffer the least and latest injury and show the slowest and poorest recovery. During the first few weeks after the beginning of massive radiation therapy, a patient's blood picture might correspond roughly to some part of the left side of the graph, labeled "Phase of Injury." The lymphocytes are most markedly depressed, the granulocytes moderately and the erythrocytes least of all. In the later stages of recovery from massive therapeutic irradiation of tissues and particularly in chronic occupational exposure, the relative blood counts are reversed. This is represented in the right side of the graph, labeled "Phase of Recovery." Moderate granulopenia is the rule, associated with relative or absolute lymphocytosis and varying grades of anemia. The eosinophils, basophils, monocytes and platelets have been omitted, since their behavior is inconstant.

The circulating cells show changes in character as well as in number. Soon after irradiation of tissues, damaged cells may be found in circulation, and subsequently immature forms of all series may appear. Bizarre

regenerative states are sometimes seen, particularly in persons subjected to chronic occupational exposure. Various degrees of lymphocytosis, monocytosis, eosinophilia and erythrocytosis have been described. Since 1911 leukemia has been reported in 24 radiologic workers. Some doubt exists as to the etiologic role of radiation in these cases even though the incidence of spontaneous leukemia in laboratory animals may be increased by radiation. No specific treatment is known for any of the blood disorders attributed to radiation.

The work reported to date has failed to establish any constant or dependable alteration in the water, sodium, chloride, calcium, phosphorus, cholesterol, nitrogen, sugar or hydrogen ion concentration of the plasma as a result of therapeutic irradiation of human beings. There appears



Injury and recovery of blood cells after radiation therapy. *L* designates the curve of the lymphocyte count; *G*, that of the granulocyte count, and *E*, that of the erythrocyte count.

to be a transient shortening of the coagulation time in many patients together with a brief drop in blood pressure. The beneficial effect of small doses of radiation on some infectious processes has not as yet been correlated with any changes in the blood plasma or cells.

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Notes and News

Awards and Grants.—The John Phillip Memorial Medal of the American College of Physicians has been awarded jointly to the late Dr. James D. Trask and to Dr. John R. Paul, associate professor of medicine, Yale University.

The Heberden Medal for research in rheumatic diseases for 1942 has been awarded to Philip S. Hench, of the Mayo Clinic, Rochester, Minn., "in recognition of his distinguished contributions to the subject over a number of years, and particularly of his most recent work on the effect of jaundice on the course of rheumatoid arthritis."

A grant of $300,000 has been made by the National Foundation for Infantile Paralysis to the Johns Hopkins University for the establishment of a center for the study of infantile paralysis and related problems.

Deaths.—Wade H. Brown, member of the Rockefeller Institute for Medical Research, at one time professor of pathology in the University of North Carolina, investigator of syphilis and of constitutional and physical factors in disease, died August 5, at the age of 64.

Society News.—At its recent annual meeting in Philadelphia, the American Society for Clinical Pathologists elected Harry Goldblatt president, Walter S. Thomas president-elect, John T. Bauer vice president, A. S. Giordano secretary-treasurer.

The American College of Physicians will hold its 1943 session in Philadelphia, April 13-16, 1943.

Indexing and Abstracting.—A joint committee is formulating the study of the most pressing problems of indexing and abstracting the literature of research fields. The committee is composed of representatives of the American Association of Law Libraries, the American Library Association, the American Medical Association, the Association of Research Libraries, the Medical Library Association, the National Research Council and the Special Libraries Association. Communications should be addressed to Mrs. Barbara Cowles, University of California Library, Berkeley, Calif.

Book Reviews

Occupational Tumors and Allied Diseases. W. C. Hueper, M.D., assistant director and principal pathologist of the Warner Institute for Therapeutic Research, New York. Pp. xxviii and 896. Price $8. Springfield, Ill.: Charles C. Thomas, Publisher, 1942.

In this large book information on occupational tumors and allied diseases is brought together, covering the incidence, distribution, causation, pathology, experimental reproduction, therapy, relation to public health, medicolegal and other aspects. The book is intended for members of the medical profession, public health workers, members of legislative bodies, members of the legal and judicial professions, industrial managers and engineers, research workers, life insurance companies and others. After an introduction, succeeding chapters are devoted to occupational tumors of the skin, the alimentary system, the respiratory system, the urogenous organs, the blood-forming organs, the mesenchymatous tissues, the eye and its adnexa, the nervous system, the endocrine glands and the sex organs.

The space is properly unevenly apportioned among these subjects. For example, 281 pages are devoted to occupational tumors of the skin and only 14 pages to those of the nervous system. While considerable space is devoted to non-neoplastic conditions about which information is available elsewhere, the inclusion of much of this material is justified. For example, it is impossible to separate a discussion of arsenical cancers of the skin from the arsenical dermatoses, hepatic carcinoma from cirrhosis and the leukemias from hypoplastic and hyperplastic conditions in the blood-forming tissues. The need for inclusion of a chapter of 56 pages on occupational tumors of the alimentary system is not at once apparent, but after reading this chapter most skeptics will probably vote their thanks to the author for his critical and scholarly analysis. Certain sections could have been shortened if the book were intended only for medical readers (e. g., the symptomatology of lung cancer), but to others such material may be valuable.

This represents one of the most ambitious examples of book writing in recent years. A wealth of material, much of which is not readily available to most medical readers, is compiled from the vital statistics of many countries, from the reports of special commissions, from the industrial literature and from many other sources. It is the opinion of the reviewer that this is one of the most valuable reference and source books which has appeared in recent years, that it is destined to become widely used and that it is assured a wide circulation because of the store of information which it contains.

Apart from other considerations the occupational cancers are important because through them the general principle of the chemical causation of some forms of human cancer was established. This principle has been accepted slowly; general acceptance should be hastened by this book. Likewise, these occupational cancers show that prophylaxis, by protective and sanitary measures, against some forms of cancer is possible.

The publisher has done an excellent job. One wishes, however, that some of the subheadings were more conspicuous. There are no illustrations, but the bibliographies are large.

The Pathology of Trauma. Alan Richards Moritz, M.D., professor of legal medicine, Harvard Medical School; lecturer in legal medicine, Tufts College Medical School; lecturer in legal medicine, Boston University School of Medicine. Pp. 386. Price $6. Philadelphia: Lea & Febiger, 1942.

After three general chapters which deal with mechanical injuries, trauma and infection, and trauma and tumors, this book passes on to special chapters, each dealing with one system. Chapters are devoted to mechanical injuries of the

cardiovascular system, the respiratory system, the alimentary canal, the liver, the gallbladder, the bile passages, the pancreas and the spleen, the urogenital tract, the central nervous system and the skeletomuscular system.

The author states that his objective was ". . . to survey the principal causes of mechanical injuries, the manner in which they operate to produce functional and organic disturbances, the pathological characteristics of the resulting lesions, the pathogenesis of their complications and sequelae and certain types of collateral evidence likely to be of medico-legal interest." He has admirably attained his objectives.

Much information, drawn from the author's experience and elsewhere, is presented clearly and authoritatively. The result is a book that is valuable and readable. The sections dealing with bullet wounds and with injuries resulting from the detonation of high explosives are especially good. In the chapter on trauma and tumors the discussion is fairly complete, but the conclusions are hazy, as is inevitable in the present state of knowledge.

It may be pointed out without detracting from the value of the book in any way that the words "pathology" and "trauma" are both used in a somewhat restricted sense. The pathologic anatomy of trauma is stressed considerably more than are the pathologic physiology and the pathologic chemistry. For example, the section on shock is very short. Mechanical trauma is stressed more than chemical and other forms of trauma.

This book is another demonstration, if any were needed, of the increasing specialization within the field of pathology as it develops. It should be useful to those who deal with trauma from the point of view of pathology, whether rarely or commonly.

The Modern Attack on Tuberculosis. Henry D. Chadwick, M.D., superintendent of Westfield State Sanatorium, 1909-1929; tuberculosis controller of the City of Detroit, 1929-1933; commissioner of public health of the commonwealth of Massachusetts, 1933-1938; medical director of Middlesex Tuberculosis Sanatorium, 1938-1941; and Alton S. Pope, M.D., chief of the bureau of communicable diseases of the department of health of Chicago, 1926-1929; deputy commissioner of public health and director of the division of tuberculosis of the commonwealth of Massachusetts. Pp. 94. Price $1.00. New York: The Commonwealth Fund, 1942.

The purpose and the scope of this little book are well stated in the preface:

> "This handbook makes no pretense of adding to the sum of our knowledge of tuberculosis. Sufficient knowledge is already available to make the eradication of tuberculosis a possibility within a few generations if the established techniques are effectively applied. The attempt has here been made to provide a concise digest of the experience of many workers and of present-day practices in a form serviceable to the health officer and administrator. Because the facilities for tuberculosis control and forms of public health organization vary so widely, even in the different parts of this country, emphasis has been placed on the principles rather than on the exact methods that have proved productive. Prevention has been a more potent factor than treatment in the reduction of tuberculosis and, at the present level of morbidity, understanding of the epidemiology of the disease is essential to the planning of an effective control program."

There are chapters on tuberculosis yesterday and today, epidemiologic aspects of the disease, diagnostic procedures, the sanatorium as a means of control and treatment, case finding in the community and a community campaign of eradication. The book will be of great value in the practical application of the knowledge physicians now have toward the eradication of tuberculosis.

Books Received

IMMUNOCHEMISTRY. William C. Boyd, Enrique E. Ecker, Michael Heidelberger, Sanford B. Hooker, Forrest E. Kendall, Stuart Mudd, L. Pillemer, Joseph E. Smadel, Theodore Shedlovsky, and Charles A. Zittle. Reprint from the Annals of the New York Academy of Sciences (**43**:33-122, 1942). Price $1.25. New York: New York Academy of Sciences, 1942.

ANNUAL REPORT OF THE SARANAC LABORATORY FOR THE STUDY OF TUBERCULOSIS OF THE EDWARD L. TRUDEAU FOUNDATION. Saranac Lake: Edward L. Trudeau Foundation, 1941.

THE FIFTY-SEVENTH ANNUAL MEDICAL REPORT OF THE TRUDEAU SANATORIUM AND THE THIRTY-SEVENTH MEDICAL SUPPLEMENT FOR THE YEAR ENDING SEPTEMBER 30, 1941. TOGETHER WITH TWENTY-FIFTH COLLECTION OF THE STUDIES OF THE EDWARD L. TRUDEAU FOUNDATION FOR RESEARCH AND TEACHING IN TUBERCULOSIS. Saranac Lake: Edward L. Trudeau Foundation, 1941.

THE JOHN AND MARY R. MARKLE FOUNDATION ANNUAL REPORT. New York: John and Mary R. Markle Foundation, 1941.

TEXTBOOK OF BACTERIOLOGY. Thurman B. Rice, A.M., M.D., professor of bacteriology and public health at the Indiana University School of Medicine. Third edition, revised. Pp. 560 with 119 figures. Price $7. Philadelphia: W. B. Saunders Company, 1942.

TEXTBOOK OF HISTOLOGY. Alexander A. Maximow, late professor of anatomy, University of Chicago, and William Bloom, professor of anatomy, University of Chicago. Fourth edition, completely revised. Pp. 695 with 562 illustrations. Price $7. Philadelphia: W. B. Saunders Company, 1942.

COLLECTED PAPERS OF THE MAYO CLINIC AND THE MAYO FOUNDATION. Edited by Richard M. Hewitt, B.A., M.A., M.D.; A. B. Nevling, M.D.; John R. Miner, B.A., Sc.D.; James R. Eckman, A.B., and M. Katharine Smith, B.A. Volume 33, 1941. Pp. 1099 with 160 figures. Philadelphia: W. B. Saunders Company, 1942.

THE MODERN ATTACK ON TUBERCULOSIS. Henry D. Chadwick, M.D., superintendent of Westfield State Sanatorium, 1909-1929; tuberculosis controller of the city of Detroit, 1929-1933; commissioner of public health of the commonwealth of Massachusetts, 1933-1938; medical director of Middlesex Tuberculosis Sanatorium, 1938-1941; and Alton S. Pope, M.D., chief, Bureau of Communicable Diseases, Department of Health, Chicago, 1926-1929; deputy commissioner of public health and director of the Division of Tuberculosis, commonwealth of Massachusetts. Pp. 94. Price $1. New York: The Commonwealth Fund, 1942.